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THE CURRENT STATUS OF THE PREGNANT CARDIAC *

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As with every endeavor in medicine, we should stop frequently to re-evaluate the old, add the new, and discard tenets which are no longer applicable. The pregnant cardiac who formerly was said to be a candidate for abortion is now able to continue through pregnancy with safety to both mother and child. This recent change in prognosis is due to a better understanding of the physiology of pregnancy, improved medical management and modern heart surgery. We feel that, when indicated, operation should be done even during pregnancy. This may be done without fear of subsequent miscarriage or excessive risk to the mother. The present accumulation of data on the pregnant cardiac supports this optimistic outlook.

The physiologic changes that occur with normal pregnancy are well known. There are increased blood volume, cardiac output, oxygen consumption, pulse rate and respiratory rate. These changes occur early in the second trimester and, except for oxygen consumption, usually start to return to normal in the last two months of gestation. The increase in blood volume is usually 30 to 50% [1-4] (figure 1). This change occurs chiefly in the plasma volume, and is associated with a reduction in the hematocrit. The heart rate normally increases 10 beats per minute in the latter part of pregnancy. The pregnant patient normally hyperventilates. Contrary to popular belief, the vital capacity remains normal or becomes slightly increased.[5] Any decrease in vital capacity must therefore be explained as cardiorespiratory disease. This decrease is often the first sign of heart failure.[6]

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We may tend to err on the side of overdiagnosis of heart disease in evaluation of the pregnant patient. Functional murmurs and marked distortion of organic murmurs may occur as a result of hemodynamic changes and physical changes such as high diaphragm and lordotic position. Spurious x-ray enlargement of the heart and minor electrocardiographic changes are frequently seen.[7] Palpitation and paroxysmal tachycardia are not infrequent in the normal pregnancy.[8-14]

Recently we were asked to see a patient regarding the advisability of patent ductus surgery. She was a 23 year old Negro female in her sixth month of gestation. Her complaints consisted of marked dyspnea on exertion, and hyperpnea. Four cardiologists examined the patient and described a characteristic machinery murmur in the second left interspace. There was 2 plus pitting edema. The heart was not enlarged, but an angio-

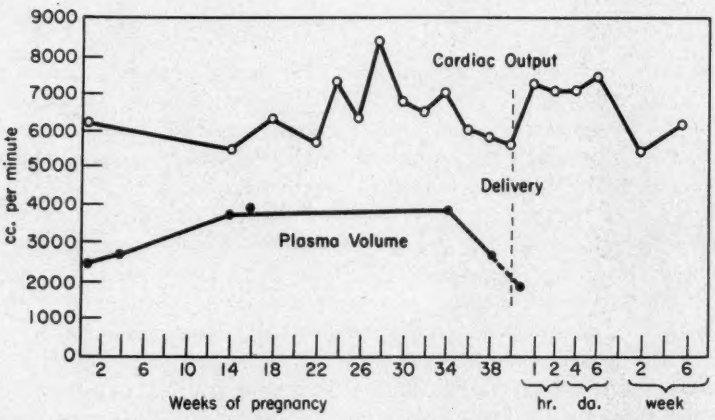

FIG. 1. Changes in plasma volume and cardiac output during pregnancy.[1, 3]

cardiogram revealed a ductus infundibulum. Catheterization studies showed no difference in oxygen content in the auricle, ventricle and pulmonary artery, and no abnormal pressure pattern. This confirmed the absence of an arteriovenous communication. Surgery therefore was not advised, and the patient was followed medically. After delivery of a normal girl, the pulmonary murmurs disappeared and did not return until the patient's second pregnancy, when she developed the same "classic murmur" as previously.

Another example of the pitfalls and difficulties in cardiac diagnosis during pregnancy is the following. A 28 year old white primipara was seen at five months gestation with hemoptysis. She had known rheumatic heart disease. A mitral systolic murmur and a presystolic rumble were present. Catheterization studies revealed no pulmonary hypertension (figure 2). The patient was followed medically through a normal pregnancy

and delivery. Subsequent bronchograms revealed a left upper lobe bronchiectasis as the source of the hemoptysis.

About 1 to 7% of pregnancies are associated with heart disease.[15-22] The over-all mortality rate for these patients is said to be 3%.[23-27a] About 85% of these cardiacs are rheumatic.[8] Of these rheumatics, 83% have mitral valve disease alone and the remaining 17% have multivalvular involvement.[8, 27b] The most common cause of death in these patients is congestive heart failure.[8, 16, 23, 28] Other causes are sepsis, pulmonary embolism, shock and hemorrhage, toxemia and subacute bacterial endocarditis. About 25% of these deaths occur during pregnancy and 75% in the puerperium.

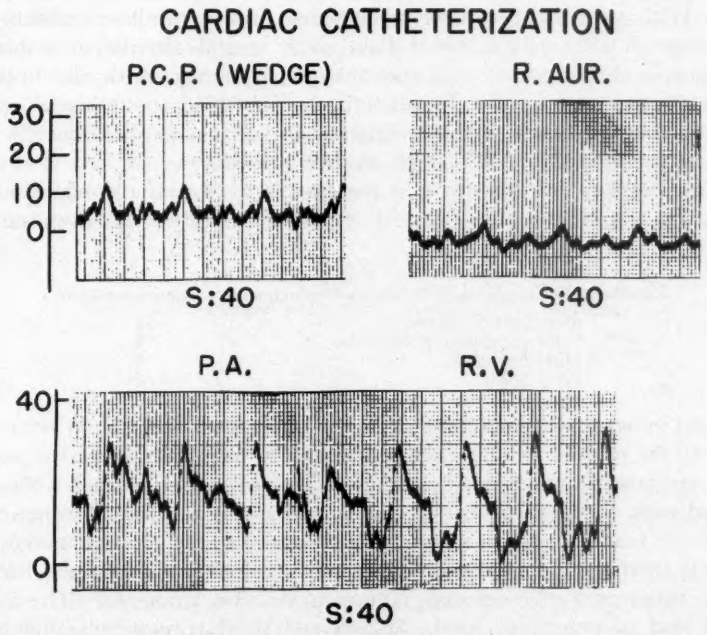

FIG. 2. Cardiac catheterization pressure curves, showing the absence of pulmonary hypertension.

For the patients with mitral stenosis who contemplate pregnancy, commissurotomy is frequently indicated. Our requirements for valvulotomy in the young married woman are (1) dyspnea on ordinary activity, (2) definite and predominant mitral stenosis (physical findings, electrocardiogram, and x-ray compatible with the diagnosis of mitral stenosis and pulmonary hypertension), (3) confirmatory catheterization findings in questionable cases. In addition hemoptysis, and/or embolization may be indications. It is not essential that patients be in class 3 or 4 cardiac status. With the contemplated increased load of pregnancy, upgrading of a cardiac

class 2 to 3 patient to one of class 1 to 2 will certainly decrease the risk of the forthcoming pregnancy. Harken and others [30, 31] have shown that the risk of commissurotomy in this type of patient is approximately 1%. Glover has stated that 50 patients who had been successfully operated on subsequently became pregnant with no maternal or fetal mortality.[32] As a result of our own experience, plus replies to questionnaires sent throughout the country, we would like to report 96 pregnancies subsequent to commissurotomy. There were no maternal deaths and only one fetal mortality (table 1).

The patient who is seen in the first trimester of pregnancy and found to have mitral stenosis and early heart failure presents a controversial problem. With very strict cardiac management, many of these patients can be delivered with only minimal risk. The second alternative would be therapeutic abortion and subsequent commissurotomy, with the hope of pregnancy reserved for the distant future. The third possibility would be mitral commissurotomy during pregnancy to improve cardiac function and decrease the mortality rate of both mother and baby.

This problem recently arose in the case of a 24 year old white female who was admitted to the hospital with severe orthopnea, dyspnea and

TABLE 1

Results of 96 Unpublished Pregnancies Subsequent to Commissurotomy

Mitral commissurotomy	96
Subsequent normal deliveries	98
Maternal death	0
Fetal death	1

cyanosis in her third month of gestation. The patient had had no symptoms prior to the present illness. She was found to have mitral stenosis and to be in severe acute congestive heart failure with pulmonary edema. She was treated with digitalis, diuretics, bed-rest and a low salt diet, and improved. The heart size returned to normal and the patient became asymptomatic on medical treatment. Commissurotomy was advised in this patient because of the occurrence of congestive failure in the first trimester. The anticipated load of pregnancy in the second and third trimesters would likely lead to recurring refractory heart failure. The valvulotomy was performed and the patient had an uneventful pregnancy, delivery and postpartum period.

Many physicians feel that patients presenting with congestive failure in the first trimester should be aborted.[33-35] Since congestive heart failure is the most common cause of death in the pregnant cardiac, this practice has been widely accepted. About 90% of the patients who develop failure during one pregnancy will have a recurrence during a subsequent pregnancy.[36] The fetal mortality is increased in the presence of heart failure about threefold.[28, 29, 36] We feel that the patient who has failure due to any heart lesion that may be improved by surgery should have the surgery in preference to abortion. Preferably, these patients should be compensated prior to surgery.

The load of surgery is probably less than the load of therapeutic abortion in the second and third trimesters. During the first four months the load of pregnancy is negligible, since hemodynamic changes do not occur until the sixteenth week (figure 1). Surgery at this time should not carry any greater risk than in the nonpregnant patient. Good anesthesia and surgical technic obviate the risk of anoxia secondary to the surgical procedure.

A second alternative would be abortion followed by a commissurotomy at a later date. Then, expectation would be that the improved cardiac status would allow a normal pregnancy. Those who support this plan feel that the load of surgery added to pregnancy is dangerous, that surgery may reactivate rheumatic fever, that the diagnosis may be in error during pregnancy because of the altered hemodynamics, and that the full benefits of surgery may not be realized immediately. We are opposed to this plan because therapeutic abortion also adds a load to the heart, even if not so great a load as does valvuloplasty. Certainly therapeutic abortion after the first trimester carries an increased risk.[37] Active rheumatic fever during pregnancy is extremely rare.[16] With the endogenous production of steroids by the pregnant woman, both reactivation of rheumatic fever and the post-commissurotomy syndrome should be quite infrequent. With our present

TABLE 2

Results of 93 Unpublished Commissurotomies during Pregnancy

		Maternal Mortality	Fetal Mortality
1st trimester	36		
2nd trimester	53	3	
3rd trimester	4		
Total	93	3	5

diagnostic tools, errors in diagnosis should be avoided. Finally, the benefits from surgery are usually quickly forthcoming, and certainly the bed-rest enforced by the surgical procedure is beneficial.

The results of surgery during pregnancy in relation to fetal and maternal mortality are important in formulating an opinion. Glover operated on six patients during pregnancy and there were five normal deliveries in this group.[38] The sixth patient had a spontaneous abortion six weeks after commissurotomy. Igna's group has operated on five patients during pregnancy and all had normal deliveries.[39] Harken has operated on 21 pregnant women. In all, we have compiled 93 unpublished cases who had commissurotomy during various stages of pregnancy (table 2). Thirty-six patients were operated upon during the first trimester, 53 in the second and four in the third. The majority of these patients were in group 2 or 3 cardiac status. There were three maternal mortalities. One maternal death occurred secondary to embolization and was not related to the pregnancy. Another occurred in the early days of cardiac surgery and was believed to be due to an anesthetic-induced arrhythmia. The third case developed

progressive mitral insufficiency and refractory heart failure following surgery. Eighty-eight live babies were delivered. The fetal mortality was due to noncardiac causes, except in two cases with congenital heart disease incompatible with life. From these cases and other reports,[41-48] we feel that many mothers and infants were saved by cardiac surgery during pregnancy. The beneficial effects from commissurotomy allow better tolerance of pregnancy, delivery and the postpartum period.

There are certain cases where surgery may be indicated but the patient refuses both heart surgery and therapeutic abortion. An 18 year old girl was first seen at five months gestation. Her complaints at this time were increasing shortness of breath on exertion, and swollen ankles. Physical examination revealed a ventricular rate of 120 per minute. The x-ray and electrocardiogram showed moderate right and left heart enlargement. She was hospitalized and treated with digitalis, diuretics, low salt diet and bed-rest. She responded to medical management and was followed to term and normal delivery. During the period of peak cardiac load (24 to 32 weeks), she was kept on limited activity and bed-rest at least half of the waking day. She was given penicillin and streptomycin for two weeks postpartum.

This case demonstrates that frequently, with careful medical management, even severe cardiacs can have successful deliveries. The patient should be seen at two-week intervals and signs or symptoms of congestive heart failure thoroughly evaluated. Venous pressure, circulation time, vital capacity and weight gain should be determined at regular intervals. These will often indicate incipient heart failure. An unusually rapid weight gain or a decrease in the vital capacity should certainly forewarn us of impending danger. All cardiac patients should have extra rest from the twenty-fourth to the thirty-second week of pregnancy. Any patient in class 3 or 4 should be immediately evaluated for hospitalization.[49, 52] Usually class 1 or 2 patients should be admitted one week prior to term. All infections, even minor ones, should be treated vigorously, because these may precipitate heart failure. Subacute bacterial endocarditis occurs in about 0.02% of the rheumatic heart disease pregnancies, and is readily treated with our present antibiotics.[19, 50] However, bacterial endocarditis is more likely to become apparent a few months following delivery. Prophylactic penicillin during delivery and the postpartum period should reduce the incidence of this complication. A minor degree of anemia during pregnancy may also be a factor in causing congestive heart failure, and should be corrected. At delivery, blood loss should be accurately measured and excessive loss replaced. Thyrotoxicosis may occur and should be treated. Anxiety of a significant degree should also be treated, by both psychotherapy and sedatives if needed.

The delivery in cardiacs is frequently premature.[51] This should favor an easy delivery. The second stage of labor should be shortened with forceps delivery. Oxytocics should not be used during delivery. Good local anesthesia and oxygen therapy during delivery are important adjuncts.

A fall in blood pressure should be immediately corrected with arterenol, blood transfusion, digitalis and other measures.

The postpartum period is a period of stress for the pregnant cardiac. The cardiac work remains somewhat elevated after delivery, accounting for some of the difficulties in the immediate postpartum period. Breast feeding should not be permitted in cases with congestive heart failure. The class 3 to 4 patients should maintain the same habits of adequate rest as during pregnancy.[52] Help in the home for care of the infant should be provided. The load of infant care and the slightly increased cardiac output may precipitate postpartum failure. The delivery and postpartum period should be better tolerated if surgery has been successful during pregnancy.

Congenital heart disease in association with pregnancy has received scant attention in the past, although this group comprises 10 to 15% of the pregnant cardiacs. The prevailing opinion 10 years ago was that cyanotic heart disease per se interdicted the advisability of pregnancy. If pregnancy did occur, immediate abortion was usually advised. With our recent progress in congenital heart surgery, we can expect more and more women with congenital heart disease to enter the childbearing age. Kerr and Sodeman reported only one fatal case in 80 deliveries in various types of congenital heart disease.[54] The largest recent study, by Espiño-Vela et al.,[55] discussed 53 congenital cardiac defects associated with pregnancy. Three deaths in this group were associated with the pregnant state. One patient with patent ductus arteriosus developed subacute bacterial endocarditis after cesarean section and died. This occurred before the age of antibiotics. One patient with an atrial septal defect went into shock and developed marked cyanosis after delivery and died. Others have reported deaths in various congenital arteriovenous communications occurring shortly after delivery. The usual sequence of events is a drop in systemic pressure, reversal of the previous left-to-right shunt, cyanosis and death. This is apt to occur in the presence of large shunts and greatly enlarged hearts if there is a sudden drop in systemic pressure following delivery.

The pregnant patient with patent ductus and a large shunt should have the ductus severed during pregnancy if this procedure was neglected prior to pregnancy. The mortality in pregnancy with patent ductus arteriosus is 3%.[19] The mortality of patent ductus surgery is less than 0.5%.[53] We have accumulated 22 unpublished patent ductus cases operated upon during pregnancy (table 3). There was no maternal mortality, and only one fetus aborted. The fetal abortion occurred one month after surgery. Most of these cases were operated upon because of large shunts and progressive dyspnea.

We recently saw a 28 year old Negro woman at four months gestation. She had had increasing dyspnea and pedal edema during the three weeks prior to admission. She also complained of palpitation and orthopnea. During her previous two pregnancies she had had similar complaints, and

had been treated for congestive failure and kept at strict bed-rest during the second and third trimesters. The symptoms were worse during her second pregnancy, and were accompanied by two episodes of syncope. She was advised to have heart surgery following her second delivery but neglected to. She was found to have a machinery murmur, though the diastolic component was much less prominent than had been described a few weeks earlier in pregnancy. This suggested less left-to-right shunt or beginning reversal of shunt. Cardiac catheterization was performed and a shunt was demonstrated. Because of the early appearance of symptoms in this pregnancy and difficulties occurring during her previous pregnancies, surgery was advised. She did well after closure of the ductus and had complete relief of dyspnea. The subsequent course of pregnancy and delivery was normal.

A second patient who had patent ductus was a 26 year old Negro woman who refused surgery during her sixth month of gestation in spite of the fact that she went into shock and became deeply cyanotic following her previous delivery. The patient did go through this pregnancy successfully with strict medical management, though she developed shock and cyanosis six

TABLE 3

Results of 22 Unpublished Cases of Patent Ductus Arteriosus Operated Upon during Pregnancy

Patent ductus operation during pregnancy	22
Maternal mortality	0
Fetal mortality	1—abortion one month post operative

hours after delivery. An intravenous drip of arterenol was given and the systemic pressure promptly rose, reversing her to left to right shunt and clearing the cyanosis.

In any case of arteriovenous shunt we should have an intravenous vasopressor agent ready in case of reversal of shunt. Blood pressure should be checked at frequent intervals so that arteriovenous rather than veno-arterial flow may be maintained.

Tetralogy of Fallot patients usually did not live to the childbearing age prior to the era of Blalock and Potts operations. Many of these patients are now reaching the childbearing age, and pregnancy in these cases now has to be evaluated. Usually patients with cyanotic heart disease are recommended for abortion. We recently reported the fourth operated case [55b] to have a subsequent normal pregnancy and delivery, and there are several others in the literature. We would like to emphasize the need for strict medical management of these patients through pregnancy and delivery. Here, as in patent ductus, systemic hypotension should be avoided with vasopressor agents to prevent reversal of shunt. We are aware of three unpublished cases who had unoperated tetralogies and successful pregnancies.

One patient had three successful pregnancies and lived to the age of 41, when she died in refractory congestive heart failure. A second case had a normal delivery at age 16. The third case had a normal delivery prior to a Blalock operation at age 29. She had a second pregnancy at age 32, at which time she had a very stormy delivery. This last case demonstrates the important

TABLE 4

Summarized Results of Several Series of Congenital Heart Disease and Pregnancy

Kaufman and Ruble	7	4	40	5	3
Espino-Vela et al.	13 [1]	2	28 [3]	6	1
Hamilton and Thomson	2	13	39 [3]	4	1
Vanderver and Kud		4	9	2 [1]	1
Kerr and Sodeman	8	6	5	5	3
Benham				46 [4]	
Lund	4	8	13 [2]		1
Bergman et al.	3	4	6		3
Mendelson and Pardee	1	4	2	3	8
Total	38 [1]	45 [0]	142 [8]	81 [5]	21 [0]
	IASD	IVSD	PDA	Coarct. Aorta	Pulm. Sten.

Figures in insert indicate maternal mortality. With present medical and surgical management, these results should be even better.

IASD—Interauricular septal defect
IVSD—Interventricular septal defect
PDA—Patent ductus arteriosus

maxim of risk increasing with the age of the patient. Patients with heart disease should certainly have their babies at an early age.

Another type of congenital heart disease which should be evaluated after surgical treatment is coarctation of the aorta. Benham [56] reported a series of 56 cases with pregnancies and found four deaths due to rupture of the aorta. Sampson [57a] and Mendelson [57b] recommended interruption of pregnancy in coarctation before the development of our present surgical technics

for this condition. There have been a few reports of resection of the coarctations with subsequent normal deliveries.[58] We have had experience with five cases of coarctation of the aorta and pregnancy. One patient had a successful pregnancy and delivery three years after resection and anastomosis of the coarctation The other four had successful deliveries without requiring surgery. Miller and Falor [58] advise surgical treatment of this lesion instead of abortion. Cesarean section is the preferable route of delivery if the pressure is quite high.[19, 51] Hamilton [19] feels that the pressure is as likely to go up as down in these cases at term, and that cesarean section should be done in resected cases.

We have also had one patient with interatrial septal defect proved by cardiac catheterization who had three normal pregnancies. One patient had congenital complete heart block and interventricular septal defect. She has had two normal pregnancies. Thus we can see that patients with many types of congenital heart disease,[55, 58-63] including cyanotic and potentially cyanotic heart disease, can have a normal delivery safely (table 4). The most important criterion in estimating how well a given patient will do is the knowledge of how well she did with her congenital anomaly prior to pregnancy. Previous heart failure, advanced age of patient, atrial fibrillation and marked cardiomegaly are ominous signs, indicating the necessity for the most careful cardiac management and evaluation of the pregnant cardiac. Any surgical procedure, such as Blalock or Brock procedure, section of a patent ductus, or excision of a coarctation defect, should be done when indicated to improve cardiac status. Cardiac surgery is known to be safe during pregnancy.

We are certain that many mothers and babies are and will be saved by assiduous medical management and, when necessary, cardiac surgical intervention. We would like to emphasize that there is no substitute for individualization, and certain patients will have stormy times despite any management. We would also like to emphasize that pregnancy has no deleterious effects on longevity of the cardiac patient. This has also been carefully documented by others.[24, 49, 52, 65]

Conclusions

1. Most hemodynamic changes of pregnancy become significant early in the second trimester.

2. The hemodynamic changes of pregnancy may greatly modify heart murmurs and other physical findings.

3. A patient with either rheumatic or congenital heart disease should be evaluated both medically and surgically early in pregnancy. When cardiac symptoms appear early and surgical improvement of the heart is possible, surgery is preferable to abortion.

4. Ninety-six patients with mitral commissurotomy subsequently became pregnant, with only one maternal and fetal mortality.

5. Ninety-three mitral commissurotomies were performed during pregnancy, with three early cases of maternal mortality, probably avoidable with present anesthesia and surgery. Eighty-eight live babies were delivered in this group.

6. Twenty-two patients with patent ductus were sectioned during pregnancy, with no maternal mortality and only one miscarriage one month following surgery.

7. Patients with various other types of congenital heart disease, such as coarctation of the aorta, tetralogy of Fallot, and interatrial and interventricular septal defects, may go through pregnancy safely.

8. Though ideally done before pregnancy, heart surgery is often a safe procedure during pregnancy for mother and baby.

9. Heart surgery is an adjunct to good medical management, and the patient should have the advantage of careful medical management through pregnancy, delivery and the important postpartum period.

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SUMMARIO IN INTERLINGUA

Nos desira relevar que le alterationes mechanic e hemodynamic, que accompania le pregnantia, pote effectuar un alteration marcate in le evalutation cardiovascular. Omne le disponibile adjutas diagnostic debe esser empleate in casos difficile, proque un correcte diagnose es indispensabile—specialmente quando on considera un intervention cardiochirurgic.

Nos opina que morbo cardiac es solmente in casos rarissime un indication contra pregnantia a termino successose. Aborto therapeutic se justifica multo rarmente per rationes cardiac. Le meticulose surveliantia del stato cardiac resultara in parturition a bon successo per patientes con mesmo sever disordines cardiac. Le rolo del chirurgia cardiac in cardiacas pregnante deveni progressivemente plus importante.

Novanta-sex patientes, qui habeva habite commissurotomias mitral, deveniva subsequentemente pregnante. Le serie includeva un morte materne e un morte fetal. In 93 altere patientes, commissurotomia mitral esseva effectuate durante le pregnantia. Iste serie includeva tres mortes materne, duo probabilemente evitabile. Octanta-octo babies vive esseva parturite. Nos opina que patientes con un historia de previe disfallimentos cardiac, patientes qui in le prime phases del pregnantia manifesta dyspnea post leve grados de effortio, e patientes con fibrillation auricular e un stato cardiac del grado 2 a 3 deriva beneficios ab un commissurotomia in despecto de lor pregnantia.

Patientes con varie congenite lesiones cardiac parturiva a bon successo. Illas includeva patientes con defectos de septo interatrial, defectos de septo interventricular, congenite bloco cardiac, tetralogia de Fallot, e patente ducto arteriose. Vintiduo patente ductos esseva sectionate durante le pregnantia del patiente. Occurreva in iste serie nulle morte materne. Occurreva un aborto un mense post le operation.

Un alte procentage del mortes materne in congenite morbo cardiac occurre al tempore del parturition. Nos desira relevar le importantia de un assidue observation del pression de sanguine. Omne reduction del pression de sanguine systemic pote esser sequite per reversion del shunt con le resultato de un morte subitanee. Agentes vasopressori intravenose debe esser constantemente al mano.

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CARCINOMA OF THE PANCREAS: A CLINICAL STUDY BASED ON 84 CASES *

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The advances in preoperative care of patients in need of extensive surgery and the more effective means of coping with infection and surgical shock have enabled skilled surgeons to report operative success in malignant disease of the pancreas. However, the operative mortality of duodenopancreatectomy in the hands of most experienced surgeons is still relatively high (Brunschwig, 26%; Waugh, 21%; Cattell, 18.5% and 7.3%).[1-3] Long-term results are even more disappointing. Of all the cases reported, only certain patients suffering from carcinoma of the head of the pancreas survived five years following pancreatoduodenal resection.[4-7]

Earlier recognition of the disease has therefore been stressed in almost every review or case report of malignant disease of the pancreas.[8-10]

The diagnosis of this disease is a challenging problem, limited by the inaccessibility of the pancreas and the lack of a method of visualizing its ductal system. X-rays may reveal displacement or alteration of adjacent organs, though usually only after the disease has progressed beyond the possibility of surgical cure.

The purpose of this study is to analyze ethnic, clinical, laboratory and pathologic features in a group of patients suffering from pancreatic malignancy and, by integration of clinical, laboratory and pathologic findings, to establish criteria for early diagnosis.

Clinical Material

Cases of malignant disease of the pancreas admitted to the Rothschild-Hadassah-University Hospital in Jerusalem (39 cases, 1944–1954), to the Hadassah Municipal Hospital in Tel Aviv (20 cases, 1947–1953), and to the Beilinson Hospital (25 cases, 1942–1952) were studied.

There were 49 males and 35 females, giving a male/female ratio of 1.4:1 (table 1).

Statistical studies on the incidence of cancer of the pancreas show that it is two to three times more common in males than in females.[8, 11, 12]

The disease appears to be much less frequent in Israelies of African and Oriental origin than in those of European origin. Only three of the 84

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TABLE 1

Age and Sex Distribution of 84 Cases of Pancreatic Cancer

	Age Groups						Total
	25–34	35–44	45–54	55–64	65–74	75–84 Years	
Males	1	5	11	13	13	4	49
Females		2	8	14	9	2	35
Total	1	7	19	29	22	6	84

patients included in this study did not come from Europe. However, from 21 to 42% of the population of Israel during the period covered by this study (1944–1954) did not originate from Europe.

Site of Lesion: The location of the malignant tumor in 63 patients was as follows: in 44 it was confined to the head of the pancreas, in two to the body of the pancreas, in eight the body and tail were involved, in two the tumor infiltrated the tail alone, while the whole gland was infiltrated in two cases. The site of the tumor in the remaining five patients could not be identified from the available records. This distribution of the sites of the lesion corresponds to reports of Duff and Pratt.[10, 12]

Analysis of Clinical Data: Of 63 cases of proved cancer of the pancreas whose hospital charts were available, the diagnosis was made on clinical grounds in 57. In six cases the diagnosis was missed. X-ray findings were of aid in establishing the diagnosis in 15 patients.

Duration of Disease: Over half of the cases had had symptoms for less than four months prior to admission (table 2). The patients with longest duration of disease complained of vague upper abdominal pain which increased during the last few months.

The most frequent symptoms listed in the case histories were:

Anorexia	51 cases	80%
Weakness and fatigue	44 cases	70%
Nausea	32 cases	50%
Vomiting	20 cases	31%
Constipation	21 cases	33%
Diarrhea	12 cases	19%

Weight loss was noted in 52 instances and ranged from 4 to 18 kg., with an average of 11 kg. There was no difference in the degree of weight loss observed in carcinoma of the head or the body and tail of the pancreas. Vomiting and diarrhea sometimes dominated the clinical picture, but a comparable degree of weight loss was observed in patients without these signs.

TABLE 2

Duration of Disease Prior to Hospitalization

Duration in months	1–2	2–4	4–6	6–9	9–12	12–60
Number of patients	20	13	6	10	3	6

Pain: Almost all of the patients in this series complained of some type of abdominal pain or discomfort. In most cases the pain was located in the midepigastrium and radiated to the back. In only three patients was the pain in the left hypochondrium. In 36 patients pain was one of the initial signs, and in 25 it was the chief complaint, while in 15 it was not a prominent sign. In eight of the patients with proved carcinoma of the head of the pancreas there was no complaint of pain.

Psychic symptoms were noted in 10 patients. Seven were in a depressed state, and one had been treated for depression and insomnia in a closed institution prior to his transfer to a medical ward. Two patients were in a state of anxiety with agitation and were very difficult to handle. In all of these patients the onset of psychic changes coincided with the onset of the other clinical symptoms. Four of the patients with psychic manifestations were suffering from carcinoma of the head of the pancreas, and in six the tumor involved the body and tail.

Physical Examination: In 52 out of 63 patients the liver was felt mainly in the right upper quadrant. In nine patients a midepigastric mass was palpated. At operation or autopsy in three of the cases these palpable masses were found to be due to the invasion of the stomach by pancreatic tumor. In five cases the masses were due to multiple metastases in the enlarged left liver lobe, while in one the pancreatic tumor itself, located in the body of the gland, appears to have been palpated.

The gall-bladder was palpable in 18 cases, while in five cases a distended gall-bladder, not mentioned in the report of the physical examination, was found at laparotomy or autopsy. Most of the palpable gall-bladders were found in jaundiced patients, confirming Courvoisier's observation of distention of the gall-bladder in obstructive jaundice caused by tumor.

Ascites was correctly diagnosed clinically in eight cases. In five additional cases various amounts of fluid were found in the abdominal cavity at laparotomy or autopsy.

Jaundice: In 46 patients jaundice appeared either at the beginning or later in the course of the disease. The designation of "painless jaundice" does not fit this disease, since the majority of the patients complained of pain. Thirty-six of the 44 patients with lesions in the head of the pancreas were jaundiced. Jaundice occurred in three of 12 cases in which the tumor did not involve the head of the pancreas, although there were no liver metastases.

Roentgenologic Examination: The indirect evidence of filling defects or displacement of adjacent organs given by x-ray examination of the gastrointestinal tract does not permit the establishment of a definite diagnosis. However, x-ray findings are sometimes striking and may be helpful in directing attention to the pancreas as the site of disease.[13-19]

Radiologic examination carried out in 62 patients yielded suggestive signs of pancreatic involvement in 15. These findings included: displace-

ment of the stomach, eight cases; gastric defects suspected of indicating benign or malignant lesion, two cases; enlargement of the duodenal loop, three cases; deformity of the duodenum (Frostberg's sign: "inverted 3"), one case; and obstruction of the duodenum, one case. It must be pointed out that the x-ray studies indicate gross changes only, and that usually insufficient attention was given to changes in motor function or alterations in the mucosal pattern. Attention to these details and newer methods might have increased the percentage of positive radiologic findings.[17, 19]

Laboratory Examinations: Blood counts: Hemoglobin determinations in 63 patients showed a mean hemoglobin concentration of 10.6 gm.%. Red cell counts in 51 patients averaged 3,700,000. Half of the cases showed a moderate anemia of 3,000,000 to 4,000,000 red cells per cubic millimeter. Six of the 51 cases suffered from severe grades of anemia, reaching in one a red cell count of 1,400,000. In most cases where there was anemia it was of the hypochromic type. However, in five it was normochromic, and in eight hyperchromic. Furthermore, most of the patients without anemia (red cell counts above 4,000,000 per cubic millimeter) also showed hypochromia.

TABLE 3

Incidence of Hyperglycemia in 63 Cases of Cancer of the Pancreas

Blood glucose, mg.%	120–150	150–200	200–300	300–
Number of cases	11	10	7	1
Mean blood glucose	131.4	165.9	251.1	(590)

About half of the patients examined showed a leukocytosis ranging up to 25,000. One exceptional case with widespread metastases had a count of 106,000 per cubic millimeter. Leukocytosis was found in all patients suffering from thrombo-embolic complications and in the majority of those with metastases.

Erythrocyte Sedimentation Rate: Only rare reference to the erythrocyte sedimentation rate in this disease is found in reviews. Brown [8] mentions that in nine out of 10 cases examined it was markedly elevated. In one case it was as high as 135 mm. after the first hour (Westergren method), and 28 cases had a sedimentation rate above 50 mm. after the first hour. Our findings indicate that increased sedimentation rate is frequently found in carcinoma of the pancreas.

Hyperglycemia and Glycosuria: Hyperglycemia of over 120 mg.% was found in 29 out of 63 patients and ranged as high as 590 mg.% (table 3). The average blood glucose in the patients with hyperglycemia was 188 mg.%. Glucose tolerance tests performed in seven patients with normal fasting blood sugar values gave a diabetic curve.

Hyperglycemia was found in 19 out of 44 cases with carcinoma of the head of the pancreas, and in 10 out of 19 with body and tail involvement, or involvement of the whole gland. This would indicate that the site of the lesion does not influence the incidence of hyperglycemia. In two series

TABLE 4

Weltmann's Coagulation Test (WCT) in 34 Patients

	Left				Normal Range				Right
WCT	1	2	3	4	5	6	7	8	
Number of cases	2	2	1	3	7	9	7	3	

reported by Joslin [20] the onset of diabetes preceded by an average of 2.6 years the first signs referable to malignant growth in the pancreas. However, diabetic symptoms preceded the onset of other symptoms of the disease in only three patients of our series by seven, two and one-half and two years, respectively. In four cases diabetes started at approximately the same time as other symptoms, while in the remaining cases hyperglycemia was detected during hospitalization. Glycosuria was found in only 15 of the 29 patients with hyperglycemia.

Amylase: The blood amylase was determined in 29 patients. Only four showed slightly increased values—133, 139, 154 and 160 Somogyi units, respectively. Urinary amylase was increased in four cases (320, 512, 640 and 1536 Wohlgemuth units). Three of these values were obtained from patients whose blood amylase values, tested the same day, were below 100 units. As in acute pancreatic disease, it appears that in malignancy of the pancreas the increase in the serum enzyme concentration is only transitory, and that deviations in amylase concentration may sometimes be found only in the urine. The positive findings were obtained from four cases with the lesion in the head of the pancreas. In eight patients with the tumor in the body alone, or both body and tail, the amylase values in the blood and urine were in the normal range. This group includes five patients with thrombo-embolic complications proved at autopsy.

Liver Function Tests: Thymol turbidity and cephalin flocculation tests performed in 25 patients were normal. Results of the Weltmann coagulation test showed a marked shift to the left in patients suffering from carcinoma of the body and/or tail of the pancreas with multiple metastases.

Cholesterol determinations were carried out in 30 cases, including 26 patients with jaundice and four without jaundice. In only one of the latter group was the cholesterol elevated (425 mg.%). The results of determinations in the 26 jaundiced patients are shown in table 5.

Values above 250 mg.% of cholesterol are considered as increased in the age groups concerned. Thus, cholesterol was found increased in 75% of the cases examined. The corresponding percentage found by Thompson [21] is 58.8% and by Greenspan and Epstein, 78%.[22] In four jaundiced patients the cholesterol-ester ratio was below 1:1.

TABLE 5

Cholesterol Values in 26 Patients with Jaundice Due to Pancreatic Carcinoma

Serum cholesterol, mg.%	Below 250	251–349	350–499	750
Number of cases	5	12	8	1
Mean value	172	321	426	

Alkaline phosphatase determinations were carried out in 27 patients. Nine patients, some of them deeply jaundiced, had values below 10 Bodansky units. Fourteen jaundiced patients showed values between 10 and 25 Bodansky units. There was no correlation between the degree of bilirubinemia and the increase in alkaline phosphatase, or between alkaline phosphatase and the height of cholesterol. Of four cases without jaundice, two showed values in the normal range; the other two had values of 25 and 40 Bodansky units, respectively. This indicates that a marked increase of alkaline phosphatase can be found in pancreatic malignancy without clinical or laboratory signs of obstructive jaundice.

Total protein determinations were carried out in 34 patients. Only 13 patients fell outside the normal range of 6.5 to 7.9 gm.%. Ten showed a decrease in total protein (average, 6.0 gm.%), and three showed higher values, up to 8.1 gm.%. Nine patients showed a normal albumin-globulin ratio (1.6–2.6). Other values obtained ranged from 0.33 to 1.55—average, 1.07. All patients with ascites had a decreased albumin-globulin ratio. However, it is noteworthy that in these cases the serum albumin values were not below 3 gm.%.

Gastric analysis was carried out in 13 patients. Achlorhydria was found in only two patients 45 minutes after the Ewald test meal. No special diagnostic aid is afforded by this examination.

Stool Examination: In 13 out of 34 patients examined, increased amounts of fat and undigested muscle fibers were found. Tests for occult blood were positive in 10 instances. The importance of stool examination in pancreatic disease cannot be overemphasized. The assumption that diarrhea is *the* sign of pancreatic disease is erroneous, since many of the cases do not present this sign.

Prothrombin determinations were performed in 27 cases. Twenty-five of these were jaundiced and showed the following results: two had normal values; in six the prothrombin level was between 50 and 75%, in eight between 30 and 50%, and in nine below 30% of the normal. Two patients without signs of jaundice, with carcinoma of the body and tail of the pancreas and multiple metastases, revealed a prothrombin level of 30 and 35%, respectively.

Thrombo-embolic Complications: In four out of 15 patients suffering from carcinoma of the head of the pancreas, autopsy findings revealed vascular involvement, including arterial embolism. In one patient, suffering in addition from generalized atherosclerosis, mural thrombi in the aorta were found. Another died of multiple pulmonary emboli, and in the third a recent splenic infarct was found. The last patient had multiple mural thrombi in the inferior vena cava and in the iliac veins.

Of 14 patients suffering from carcinoma of the tail or body and tail of the pancreas, only four had no thrombo-embolic complications. The other 10 patients showed thrombi on the mitral valves (three cases), on the aor-

tic valves (two cases), in the vena cava inferior (two cases), single and multiple pulmonary emboli (two cases), and emboli in spleen and kidney (two cases).

The incidence of thrombo-embolic complications in this small group is rather high. With the lesion in the head of the pancreas, 26% of the cases had thrombo-embolic complications; with the lesion in the body and/or tail of the gland, 70% had this complication. In the latter group, multiple thrombi were observed in five patients.

Discussion

In the search for etiologic factors in malignant disease, the epidemiologic approach has stimulated theories of causation. Thus, the high incidence of malignant disease of the pancreas among natives of Uganda has been attributed to undernutrition.[28] In this study the difference in the morbidity rates of the various ethnic groups in Israel is evident. Undernutrition cannot be assumed to play an important role, since the nutritional standards of our patients, originating from European countries, are usually much higher than those prevailing in communities originating from the Near and Far East.

Of the 84 cases included in this study, we did not observe the reported increased prevalence among males. Rogers and Thompson in their series also report a ratio of 1.5:1. However, for cases of carcinoma of the body and tail of the pancreas the ratio of males to females was 2.1:1. For lesions in this site Smith and Albright [9] found five times as many males as females, and Strang [10] reported a male-to-female ratio of 2.2:1.

The average age of patients with carcinoma of the body and tail was found by Levy and Lichtmann [24] in 19 cases to be lower than that in the cases of carcinoma of the head of the pancreas. In our material the average age for males was the same for both sites (57.5 years), while for females it was 64 years for lesions in the body and tail, compared to 59.8 years for lesions in the head of the pancreas.

Although there is no histologic or functional differentiation between the head and the body and tail of the pancreas, the classification of the clinical material by the site of the tumor is most valuable in analyzing the various symptom complexes. Chauffard, in his classic description of malignant disease of the pancreas, refers to carcinoma of the head of the pancreas as "pancreatico-biliaire," because of associated jaundice, and to that involving the body and tail as "pancreatico-solaire," because of the involvement of the solar plexus, causing pain.[25] In our analysis of clinical signs this differentiation is well marked by the high incidence of jaundice in patients suffering from carcinoma of the head of the pancreas (81.8%) as compared to the lower incidence of jaundice in tumors developing in the tail or body and tail (25%).

As for pain, the differentiation was not so marked. While all patients with lesions in the body and/or tail of the pancreas had pain, the majority

of those with the lesion in the head of the pancreas also had pain (82%). Thus, "painless" jaundice does not appear to be a reliable sign in the differential diagnosis of obstructive jaundice. Pain as an initial sign was recorded in all patients suffering from carcinoma of the body and tail of the pancreas. In nine out of 12 cases it was the chief complaint, whereas in carcinoma of the head of the pancreas pain was the chief complaint in 16 cases (36.3%). The episodes of pain, sometimes continuous, were usually unrelated to food and were localized in the right, middle or left hypochondrium, according to the site of the lesion, and in most cases radiated to the back.

Regardless of the site of the lesion, loss of appetite, weight loss and weakness were the most constant findings in our case histories, and frequently even preceded jaundice or pain.

An additional sign of diagnostic importance is thrombosis, which is frequently encountered and may even be an initial complaint. Single or multiple thrombotic phenomena in a patient over 50 years of age suffering from an ill defined disease should suggest neoplastic disease of the body and tail of the pancreas. Sproul [26] has drawn attention to the high incidence of venous thrombosis in patients suffering from carcinoma of the pancreas, particularly of the body and tail. The incidence of thrombosis observed in this series—70% for lesions in the body and tail, and 26% for lesions in the head of the pancreas—is even higher than those reported by Sproul. Various explanations have been offered for the frequency of thrombo-embolism as a complication of pancreatic carcinoma.[27, 28, 29] Malignancy per se is apparently not responsible, since in carcinoma of other organs these complications are much less frequent. Furthermore, the difference in incidence of thrombosis in pancreatic carcinoma affecting the head or involving the body and tail indicates the significance of the situation of the lesion itself. In addition, metastatic tumors in the pancreas derived from other organs are also accompanied by an increased incidence of thrombo-embolism.[28] The convincing hypothesis of Gore relates the variations in the incidence of thrombo-embolism, depending upon the site of the tumor, with atrophy of the body and tail of the pancreas due to increasing pressure on the duct of Wirsung. When carcinoma of the head of the pancreas leads to such atrophy, the production of trypsin ceases. However, when the body and tail alone are affected, there is a chronic inflammatory reaction in the tumor bed, with disruption of acinar units, and trypsin as well as other enzymes are continuously released into the circulation. Since under certain conditions trypsin is known to have thromboplastic activity, it may be the agent responsible for the frequent thrombo-embolic complications. Another factor affecting thrombosis is the breakdown of the antitryptic mechanism, which counteracts the effect of circulating trypsin.

Our finding of a relatively high incidence of thrombosis in patients with carcinoma of the head of the pancreas might be explained by the existence of an accessory pancreatic duct draining active secreting pancreatic tissue.

A second possible explanation is that a tumor developing in the head of the pancreas, like one in the body and tail, causes a chronic, smouldering, inflammatory reaction, with continuous release of enzymes into the circulation, until complete compression of the duct abolishes secretory activity. As with tumors developing in the body and tail of the pancreas, breakdown of the antitryptic mechanism might lead to thrombosis.

Physical examination revealed enlargement of the liver in 82.5% and distention of the gall-bladder in 36.5% of our patients. While half of the patients with jaundice had a distended gall-bladder, the absence of this finding does not exclude pancreatic cancer. The low incidence of distention of the gall-bladder can be explained by extension of the tumor and obstruction of bile ducts above the junction of the cystic duct, or by previous gall-bladder disease. Mikal and Campbell [29] point out that dilatation of the common bile duct is more often related to carcinoma of the pancreas than is distention of the gall-bladder. The recently introduced intravenous cholangiography, which visualizes the biliary ducts, independent of the function of the gall-bladder, promises to be a valuable aid in diagnosis of the site and possibly of the nature of choledochal obstruction in patients with mild or moderate jaundice. In every patient under investigation for carcinoma of the head of the pancreas, radiologic examination should include intravenous cholangiography as well as barium studies of the gastrointestinal tract.

Outlining the pancreas by inflation of the stomach [15, 18] or by presacral air insufflation and tomography [19] cannot be expected to be of aid in early diagnosis, since small lesions will not be discovered by these methods. In general, we feel that the early-diagnosis slogan is overemphasized in pancreatic cancer, since the prognosis is mainly dependent upon the histologic type of the tumor. The many lymphatic channels available to tumors of the pancreas predispose to early, widespread metastasis. Thus recent studies on the anatomy of lymphatics of the human pancreas indicate that even more radical resection than that undertaken currently for cancer of the head of the pancreas, including resection of superior mesenteric and midcolic vessels, may have to be carried out if better results are to be achieved.[30]

Laboratory Findings: Anemia was found more frequently (in about 60%) than was reported by Berk and others.[31] The mean values for our patients with carcinoma of the body and tail reveal a red cell count of 3,600,000 per cubic millimeter and 10.5 gm.% hemoglobin, contrary to statements that anemia is rare in tumors developing in the body and tail.[24] No free bleeding from the gastrointestinal tract is mentioned in the case histories of our patients. Smith and Albright [9] found anemia in 81% of their cases.

One of our patients who was suffering from widespread metastases originating from a tumor of the pancreas showed a leukemoid reaction, with a leukocyte count of 106,000. Such counts have been observed occasionally in carcinoma of the stomach or colon.[32]

In a high proportion of our patients there was a considerable accelera-

tion of the erythrocyte sedimentation rate even after correction for anemia. Unexplained anemia and a real increase in sedimentation rate in patients above the age of 50 with ill defined complaints are, in the absence of infection, highly suggestive of malignant disease. A thorough investigation of the gastrointestinal tract in the search for a tumor should be started without delay.

Hyperglycemia and Glycosuria: There is a certain amount of confusion in the literature as to the influence of the site of the lesion on the incidence of hyperglycemia. While some authors found that hyperglycemia occurs much more frequently when the lesion develops in the head of the pancreas, others report the higher incidence in involvement of the body and tail. Our data show an almost equal incidence in both sites. Since hyperglycemia occurs in so many cases of carcinoma of the head of the pancreas in which the islets in the body and tail are not functionally affected, destruction of islets due to tumor cannot be a primary cause of the disturbance of carbohydrate metabolism. Steroid hyperglycemia is an attractive explanation,

TABLE 6

Disturbed Carbohydrate Metabolism in Pancreatic Carcinoma

Author	Site of Lesion	Hyperglycemia	Glycosuria
Brown et al.[8]	All sites	55.5%	20.0%
Authors' data	All sites	46.0%	23.8%
Thompson and Rogers[21]	All sites	25.6%	17.4%
Berk[31]	All sites	19.4%	9.4%
Arkin and Weisberg[38]	All sites	15 %	
Smith and Albright[9]	Body and tail	8.1%	
Strang and Watson[13]	Body and tail	—	1.8%
Katsch[32]	Body and tail	33.0%	
Authors' data	Body and tail	52.6%	

since considerable stress accompanies this disease, in which severe and constant pain affects a considerable proportion of its victims. Another possible explanation is that small amounts of trypsin released into the circulation, due to the disruption of acinar units in the tumor bed, may inactivate insulin furnished by intact islet cells.

In general, the common liver function tests were not helpful in diagnosis. Of interest is the occasional finding of high serum alkaline phosphatase in patients without biliary obstruction. Since alkaline phosphatase is secreted by the duct cells of the pancreas as well as the liver, obstruction of the main pancreatic duct alone may divert this enzyme into the blood stream.[34]

The rarity of steatorrhea may be explained by the frequency of anorexia, with aversion to fatty food in particular. However, when fat is added to the diet, bulky stools appear promptly. Thus, the examination of the stool for fat and protein utilization while giving a full diet seems very important for the detection of pancreatic insufficiency. Essentially similar information may be derived from a secretin test. However, the inconvenience of

duodenal intubation of severely ill and elderly patients limits its use as a routine procedure.

Enzymes: Increased amylase values in pancreatic carcinoma have been reported by a number of authors.[35, 36] Although the incidence varies considerably (10 to 41%), the discrepancy may be related to the stage of disease.

Serum lipase activity has been found by different authors to range from 40.5 to 75%.[35, 37] Since the different pancreatic enzymes are secreted in constant proportion to each other, they would be expected to be present in the serum in the same proportions. The discrepancy between the frequent finding of elevated lipase and the lower incidence of elevated amylase values has yet to be explained.

The third main pancreatic enzyme, trypsin, has been implicated in explaining the high incidence of thrombosis in this disease.[28, 29, 40] Experimental data [41–44] indicate that rapid intravenous administration of trypsin is followed by massive intravascular coagulation, while slow injection is accompanied by transitory depletion of prothrombin and fibrinogen, which may lead to hemorrhage. In vitro trypsin in small amounts promotes coagulation of blood by conversion of prothrombin to thrombin. In the natural course of malignant disease of the pancreas no sudden release of trypsin has been reported. However, Ratnoff [45] noted a fatal hemorrhagic state associated with excessive plasma proteolytic activity in a patient suffering from carcinoma of the head of the pancreas. The low prothrombin values found in patients without severe liver damage or prolonged jaundice may be due to the transitory or constant depletion of prothrombin following the slow release of trypsin into the blood stream. The increased trypsin level enhances the production of antitryptic substances which complicate the technic of determination of trypsin in the serum. This is the main reason why clinicians rely chiefly on determinations of amylase and lipase, which are easily obtained from the laboratory. In addition to the role of trypsin in blood coagulation, we have also pointed out its potentially destructive effect on insulin, as a possible explanation of the hyperglycemia so frequently observed in cancer of the pancreas. More research on this problem is obviously needed to reach full understanding of the significance of continuous release of trypsin into the circulation.

Summary

The clinical and laboratory data of 84 cases of carcinoma of the pancreas collected from three hospitals in Israel were analyzed. The significant findings included the observation that this disease occurred mainly in Jews originating from European countries, and rarely in those from Oriental countries.

Anorexia and loss of weight were the most frequent symptoms. The

classic diagnostic syndrome of painless jaundice was rarely observed. Psychic symptoms occurred in 10 patients. Only about 50% of the patients with jaundice had a distended gall-bladder.

Increased sedimentation rate was a very frequent finding. Hyperglycemia and positive glucose tolerance tests were observed in almost half of the patients, and were not correlated with the site of the lesion in the pancreas. External pancreatic insufficiency developing in the course of disease and proved by stool examination was found in 38% of the cases examined. Serum amylase determinations were found to be of limited value.

Radiologic examination pointed to the correct diagnosis in 25% of the cases.

The extremely high incidence of thrombo-embolic phenomena, especially in carcinoma of the body and tail of the pancreas, is stressed as an important sign, and the role of trypsin in the thrombo-embolic process is discussed.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Es presentate un analyse del aspectos ethnic, clinic, laboratorial, e pathologic observate in 84 casos de carcinoma primari del pancreas. Esseva constatate que le morbo es principalmente prevalente in judeos originari del paises de Europa e occurre rarmente in judeos ab paises oriental e african. Perdita de peso, anorexia, e debilitate esseva—a parte le dolores—le symptomas incontrate le plus frequentemente. Alterationes psychic coincideva in 10 patientes con le declaration de altere symptomas clinic. Jalnessa appareva principalmente in patientes con lesiones in le capite del pancreas. "Jalnessa non-dolorose" esseva observate solmente in casos infrequente. Solmente circa un medietate del patientes con jalnessa habeva un distendite vesica biliari. In 15 ex 62 casos le examine radiologic del vias gastrointestinal indicava le affection del pancreas per revelar un displaciamento e deformitates de organos vicin. Le examine laboratorial monstrava frequentemente un accelerate sedimentation. Hyperglycemia esseva trovate in quasi un medietate del patientes, sin reguardo al sito del tumor intra le pancreas. Augmentate nivellos del cholesterol seral esseva trovate in 75% del casos examinate. Phosphatase alcalin del sero esseva augmentate in le majoritate del patientes con jalnessa e solmente in duo patientes sin jalnessa. Esseva constatate nulle correlation inter le nivellos de cholesterol, phosphatase alcalin, e bilirubinemia. Externe insufficientia pancreatic, demonstrate per le examine del feces, esseva evidente in 38% del casos examinate. Le importantia de iste simple test es sublineate. Determinationes de enzyma pancreatic in le sero indicava le presentia de un disordine pancreatic solmente in casos infrequente. Phenomenos thrombo-embolic complicava le curso del morbo in 10 ex 14 patientes suffrente de carcinoma del corpore e del cauda del pancreas e in quatro ex 15 patientes in qui le sito del morbo esseva le capite del pancreas. Es discutite le rolo del deviation de trypsina que es liberate continuemente a in le circulation como causa del alte incidentia de thromboses.

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ACUTE PANCREATITIS: A CLINICAL REVIEW OF 72 ATTACKS OCCURRING IN 54 PATIENTS *

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Since its recognition as a clinical entity, acute pancreatitis continues to be a thorn in the flesh of diagnostic and therapeutic medicine. Although more than a quarter of a century has passed since Elman, Arneson and Graham [1] found an elevation of the serum amylase to be of diagnostic significance, and although elaborate tests for pancreatic dysfunction have been developed, the initial diagnosis of acute pancreatitis today is missed in 65 to 75% of cases. Our lack of knowledge concerning this malady is further betrayed by the multitude of theories attempting to explain the pathogenesis and subsequent treatment. In order to avert sometimes disastrous surgery during the acute phase of pancreatitis, the diagnosis is of prime import and must be made early and with certainty.

It is the purpose of the present study to review the clinical records of all proved cases of acute pancreatitis seen at our institution over the 16 years from 1940 through 1955. Our purpose in reviewing these cases is to describe the symptomatology, physical findings, diagnostic methods, therapy, morbidity and mortality; to emphasize the value of certain laboratory tests that, while not pathognomonic, are of definite help in enabling the clinician to make a correct diagnosis; to discuss the implications of jaundice during attacks of pancreatitis, as well as the relatively frequent occurrence of diabetes mellitus as a direct complication of the disease, and to describe the preferred method of treatment.

All records of patients diagnosed as having acute pancreatitis during the period from 1940 through 1955 were reviewed. Only those cases with objective proof of diagnosis were included in this study. Proof of diagnosis was considered adequate only if, in addition to the clinical history, one or more of the following criteria were met: (1) elevated serum amylase, (2) elevated serum lipase, or (3) surgical or autopsy demonstration of either hemorrhagic pancreatitis or pancreatic fat necrosis.

Results

Sachar and Probstein [2] noted an incidence of 10 cases of acute pancreatitis in 600 autopsies at the Jewish Hospital of St. Louis. Our own inci-

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dence has not been calculated because of the large number of well patients, industrial and otherwise, entering our institution for medical examinations. That the incidence bears a direct relationship to the index of suspicion is well exemplified by our own figures. During the preliminary study covering the years 1940 through 1953, we could find only 42 well documented attacks occurring in 32 patients. In the next two years we were able to add 30 attacks in 22 new admissions. Our series comprises these 72 attacks noted in 54 patients.

History

Pain varying from moderate to severe was the chief complaint in 100% of the cases. The majority complained of mid- or right epigastric pain of a nonrelenting, boring character, with frequent radiation to the subscapular area. Ten patients complained of left upper quadrant pain, a few with radiation to the left shoulder; one had only substernal pain, and was misdiagnosed as having an acute myocardial infarct; one complained only of right lower quadrant pain.

Nausea and/or vomiting were present in all but nine attacks. There was nothing characteristic in the emesis.

Bowel habit changes were noted in 14 (19.4%) of the cases, and consisted of constipation or obstipation in all cases. No patient had diarrhea during an acute episode of pancreatitis.

Precipitating causes consisted of a heavy or fatty meal in 24 attacks. Twelve episodes were ushered in on the heels of a drinking spree, and one fatal case was the direct result of trauma (following a steering wheel injury).

Status of the extrahepatic biliary tree at the time of the initially observed attack was determined by x-ray, operation or autopsy in 44 of the 54 cases, and revealed that 21 had a normal patent biliary tree without stones, while 23 had evidence of past or present disease. Eleven of the latter group had gall-stones, two had combined gall-bladder and common duct stones, two had common duct stones, and eight had either previous or subsequent repeated nonvisualizations of the gall-bladder. Four patients had had a previous cholecystectomy for stones.

Clinical Diagnosis

The immediate diagnosis of pancreatitis is more often missed than made, and our series is no exception. The possibility was considered in 35 of the 54 original admissions; however, it was first choice in only 16 (29.6%). Six patients were diagnosed at exploratory laparotomy because the possibility of pancreatitis had not been considered preoperatively.

The two conditions most frequently confused with pancreatitis in our series were found in 20 cases originally thought to be acute biliary colic, and six cases presumed to be either penetrating or perforated peptic ulcers. The remainder of missed diagnoses ran the gamut of conditions capable of causing acute abdominal pain.

Physical Findings

Fever of significant degree was noted in only 31 of 72 attacks (43%) at the time of admission.

Dehydration and/or shock were present at the time of admission in 23 of 72 attacks (31.9%).

Tenderness was present in 66 of the 72 instances; however, associated rigidity was present in only 24 of these.

Palpable mass was noted in five cases and consisted of a hydropsed gallbladder in three, a pseudocyst from a previous attack and an omental hematoma in one.

Bowel sounds. Much to our chagrin, a chart record of bowel sounds on admission was found in only 25 of the 72 cases; however, 12, or 48% of those examined, had absent bowel sounds.

Turner's sign was not seen in a single case.

Laboratory Studies

Specific Diagnostic Tests: In the absence of surgical or autopsy confirmation, the diagnosis hinges on demonstrating a significant elevation of either the serum amylase or the lipase. Elevation of urinary levels is likewise useful, but such determinations are not done in our laboratory.

Fifty-four of 72 patients showed a significant rise of serum amylase during the course of pancreatitis, while 27 of 35 cases tested had elevated serum lipase levels. Had the proper diagnosis been considered early enough in many cases, we feel these figures would be even higher.

Nonspecific Aids to Diagnosis: While in no way pathognomonic of acute pancreatitis, certain laboratory and x-ray abnormalities occur with sufficient frequency that their presence during acute episodes of abdominal pain should suggest the possibility of pancreatitis.

X-ray: In the absence of pancreatic calculi, which are pathognomonic of existing chronic pancreatitis, two additional findings should alert the examiner to the possibility of considering the diagnosis of acute pancreatitis: (1) localized small bowel ileus as seen on the abdominal "scout film," and (2) segmental or "platelike" atelectasis in the basilar lung fields on routine admission chest films.

Of 35 admission abdominal scout films, 11 revealed a local segment of dilated small bowel, usually in the left upper quadrant; one revealed right upper quadrant calculi, presumed to be gall-stones, and one revealed pancreatic calculi.

All surviving patients had a chest film done at some time during their course of hospitalization. Five patients revealed segmental atelectasis, and two had acute pulmonary congestion (figures 1–3).

Serum Bilirubin: Twenty-one of 54 patients (39.7%) had elevated serum bilirubin levels at some time during the course of an acute attack of pancreatitis. While edema of the head of the pancreas may have caused

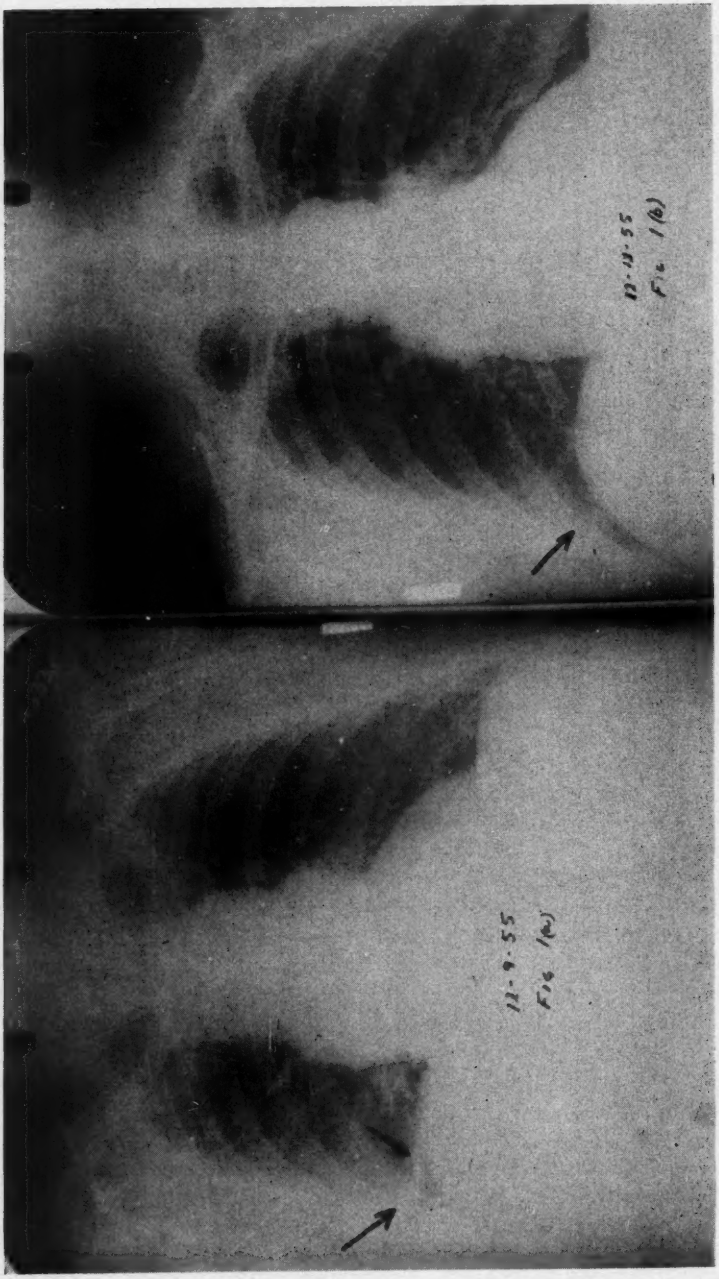

FIG. 1. Admission chest film with acute pancreatitis showing linear atelectasis on day of admission (*a*) and complete clearing three days later following cessation of acute abdominal pain (*b*).

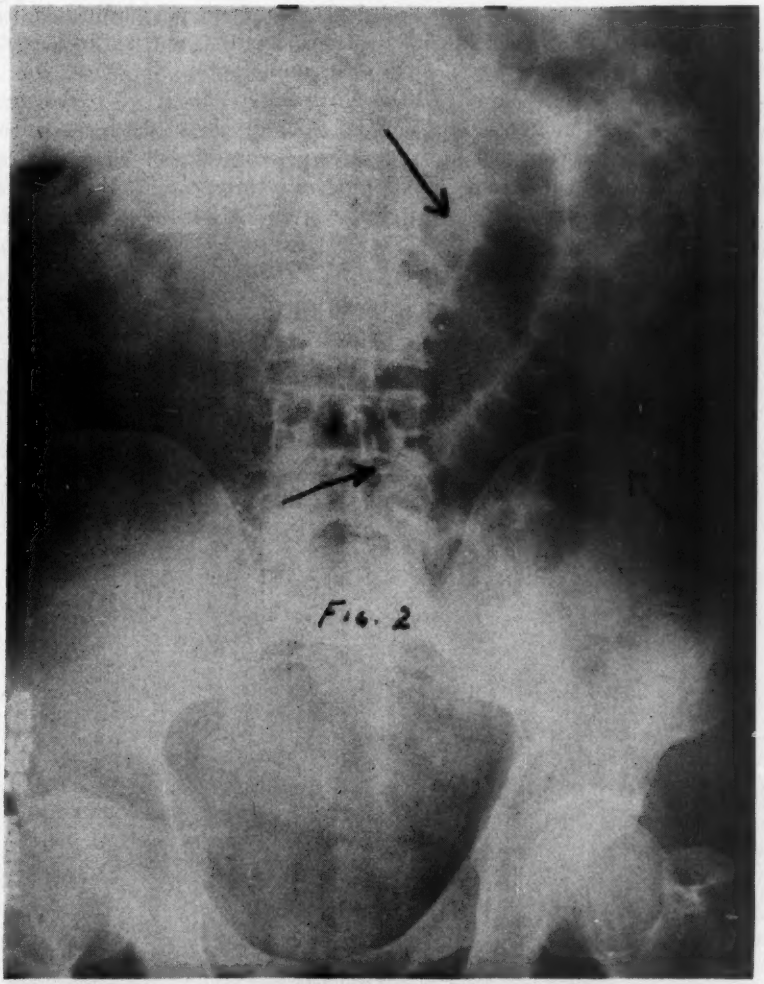

FIG. 2. Admission abdominal film in case of acute pancreatitis, showing localized small bowel ileus. There were no clinical signs of bowel obstruction.

jaundice by extrinsic compression of the common duct, it was extremely interesting to us that 17 of our 21 cases exhibiting jaundice were subsequently proved to have a surgically correctable lesion of the extrahepatic biliary tree (i.e., acute cholecystitis with stones, choledocholithiasis, or stricture of the common duct). Unfortunately, complete liver function tests were not performed, nor were any liver biopsies done, so no statement can be made concerning the possibility of coexisting hepatitis or cholangitis as a cause of the hyperbilirubinemia.

Altered Glucose Metabolism: Transient changes in glucose metabolism are well known in association with acute pancreatitis, and permanent diabetes mellitus is accepted as an occasional complication.

Glycosuria was noted in only 18 of 72 attacks (25%), whereas hyperglycemia was noted in 38 attacks (52.8%). The apparent discrepancy here is due in part to the fact that in some cases urine specimens were obtained only on admission, while some of the moderate elevations in blood sugars

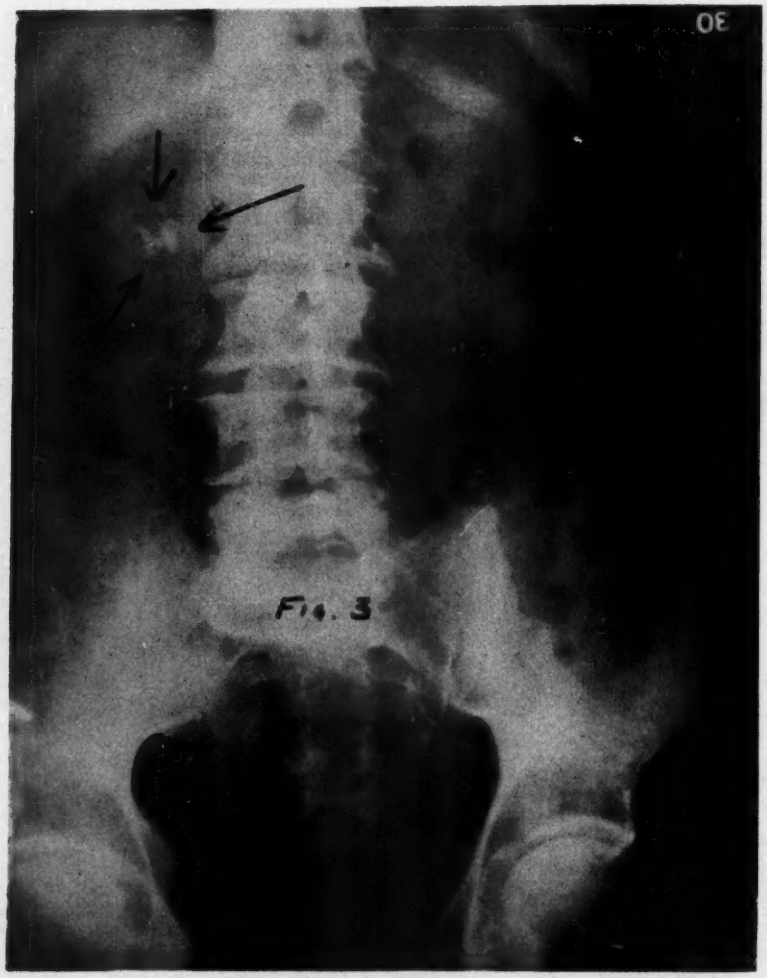

FIG. 3. Abdominal film of elderly male with recurrent pancreatitis, showing calcification opposite second lumbar vertebra. Subsequent gastroduodenal x-ray revealed this to be in area within duodenal loop localizing it to the head of the pancreas.

were not of a degree sufficient to overcome the renal threshold and cause glycosuria.

Of the 45 survivors, nine (20%) have developed permanent diabetes mellitus of all grades of severity. A previous review of the first five of those who developed diabetes,[3] and a subsequent appraisal of the remaining four, have indicated that those patients in whom an immediate effort was made to control the hyperglycemia with insulin during the acute attack developed a milder and more easily controlled diabetes subsequently. A few are now controlled on dietary therapy only. The others, from whom insulin was initially withheld, have become "brittle" diabetics.

Patients in whom multiple blood sugars were determined demonstrated a very wide swing in levels, one patient having a low of 80 mg.% and a high of 490 mg.% during one acute episode. Suffice it to say that any previously known nondiabetic who demonstrates either glycosuria and/or hyperglycemia in the face of acute abdominal pain must be suspected of having pancreatitis.

TABLE 1

Early Complications

Deaths* as a direct result of the disease	8
Pancreatic abscess or pseudocyst	4
Postoperative wound infection	3
Myocardial infarction (postoperative)	1
Acute myocardial failure	1
Venous thrombosis	
Peripheral	1
Mesenteric	1

* All fatal cases were autopsied and showed either hemorrhagic pancreatitis or areas of fat necrosis.

Other Less Suggestive Signs: In addition to the above described suggestive findings in pancreatitis, the following laboratory tests were frequently abnormal: *Leukocytosis* above 12,000 was noted in 79% of the cases. *Albuminuria* was present in 63.9% of the attacks. *Electrocardiographic* tracings showed abnormal nonspecific changes in 12 of the 20 cases in which they were done. These changes usually consisted of one of the following: depressed ST segments, slurring of ventricular complexes, and inverted, diphasic or low amplitude T waves. It is interesting that, of eight of our fatal cases, five had electrocardiograms done and all were abnormal.

MORBIDITY, MORTALITY AND THERAPY

Fifty-two attacks were managed solely by medical treatment, with a morbidity measured in terms of hospital days averaging 9.4 days. Five (9.6%) died as a direct result of pancreatitis.

Twenty patients were operated on at some time during their hospitalization and, of these, three (15%) died in the postoperative period. Five of the operations were emergency laparotomies, done because the correct diagnosis had not been considered preoperatively. One died on the fifth post-

operative day, and the four survivors averaged 25 days in the hospital postoperatively, all running a stormy course.

The remaining 15 cases subjected to surgery were operated upon during convalescence for the correction of biliary tract disease (stone or stricture). Even though surgery was deferred until the acute episode of pancreatitis had subsided, the average hospital stay of these patients was 29.5 days, the postoperative time averaging 19.8 days. Two of these patients died following operation.

It is apparent that those patients requiring surgery after pancreatitis were exposed to two to three times the mortality and morbidity of the medically managed patients.

Late Complications: Recurrence: Ten patients had a total of 18 attacks of recurrent pancreatitis. Four of these followed excessive alcoholic intake, and two were preceded by a fatty meal. One patient had severe generalized arteriosclerosis.

Three patients developed chronic pancreatitis as evidenced by pancreatic calcification on abdominal x-ray.

Diabetes Mellitus: Nine of 45 survivors developed permanent diabetes mellitus. In none of these was there a previous personal or family history of diabetes.

Final follow-up and late results revealed that eight had died during hospitalization and one subsequently of unrelated causes. Twelve were lost to follow-up, and the remainder had been followed from one month to 16 years, 20 patients for more than a year.

Ten patients had one or more recurrent attacks; however, 24 eventually became symptom free as far as upper gastrointestinal distress was concerned.

Preferred Method of Treatment

When the diagnosis has been made with reasonable certainty, medical management is to be preferred. Surgery should be reserved for complications or the correction of associated biliary tract disease and, if the patient's condition permits, should be delayed well into convalescence.

In general, the preferred medical therapy consists of the following procedures: (1) correction of fluid and electrolyte balance and the administration of whole blood, plasma or plasma expanders or albumin to combat shock (particular attention being paid to correction of calcium deficits in addition to the usual electrolytes); (2) relief of pain with Demerol or splanchnic block if necessary; (3) an attempt to antagonize the usual stimulation and ability of the pancreas to secrete, by use of gastric suction, anticholinergics and antacids; (4) administration of broad spectrum antibiotics where indicated.

In addition to the above plan of general treatment, we believe that insulin should be given to control hyperglycemia when present. In our own series, the early administration of insulin seemed to exert a protective effect on the severity of subsequent diabetes.

We have had no experience to date with the use of adrenal corticoids or ACTH in the treatment of pancreatitis.

Summary

A clinical review of the problem of acute pancreatitis has been presented, with particular reference to diagnosis, management and complications. Emphasis has been placed on many of the suggestive signs of the disease, the implications of jaundice and the relatively high incidence of diabetes mellitus occurring as a complication. The relative merits of medical therapy have been stressed, and the judicious use of insulin has been suggested for the control of the associated hyperglycemia.

Summario in Interlingua

Es presentate un revista de 72 attaccos de pancreatitis acute, occurrente in 54 patientes. In omne le casos le diagnose esseva verificate per (1) le constatation laboratorial de elevate nivellos de amylase e lipase seral o (2) un confirmation al intervention chirurgic o al necropsia. Le situation clinic al tempore del hospitalisation esseva varie grados de dolor abdominal o dorsal in 100%, associate—in 85% —con nausea e vomito. A parte le discussion del classic anormalitates laboratorial, le presente reporto sublinea le importantia de certe signos secundari que es de valor proque illos pote suggerer le possibilitate de pancreatitis. Tal signos es alterationes electrocardiographic, glycosuria, hyperglycemia, jalnessa, ileus segmental del intestino tenue, e atelectasis pulmonar segmental. Le constatation de calcification in le pancreas es pathognomonic de pancreatitis chronic o recurrente.

Le constatation de jalnessa esseva associate quasi invariabilemente con le coexistentia de un chirurgicamente corrigibile lesion del tracto biliari (calculos o strictura).

Albuminuria esseva trovate in 63,9% del casos, e glycosuria in 25. Hyperglycemia esseva notate in 52,8% del attaccos, e 20% del superviventes disveloppava subsequentemente clinic diabete mellite. Nulle de iste patientes habeva un historia personal o familial de diabete.

Le uso judiciose de insulina pro subjugar le episodios de hyperglycemia que es associate con pancreatitis es discutite favorabilemente.

Le morbiditate inter patientes subjicite a interventiones chirurgic—si intentionalmente o accidentalmente in consequentia de un incorrecte diagnose pre-operatori—esseva inter duo e tres vices illo del gruppo subjicite al tractamento medical. Le mortalitate chirurgic esseva un vice e medie le mortalitate medical.

Le autores recommenda un tractamento medical conservatori pro le regulation del stadio acute del morbo. Durante le periodo de convalescentia le arbore biliari deberea esser investigate meticulosemente. Si indicate, un operation elective pote alora esser effectuate.

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ATRIAL SEPTAL DEFECT WITH MITRAL VALVULITIS: CLINICAL AND CATHETERIZATION DIAGNOSIS *

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CRITERIA for the clinical differentiation of atrial septal defect in combination with mitral valvular disease from isolated septal defect have been suggested, based upon the degree of cardiomegaly and the size of the pulmonary conus.[1, 2] The presence of a low-pitched rumbling apical diastolic murmur, presumably due to mitral valvular disease, has also been thought to be diagnostic of the combined lesion in cases in which the diagnosis of atrial septal defect had been established physiologically. This attitude was fostered by early studies of the autopsied cases of atrial septal defect reported in the literature which indicated a high incidence of associated mitral disease.[2]

It has been shown recently on the basis of clinical and autopsy studies that an apical diastolic rumble, considered characteristic of mitral stenosis in other situations, may well be "functional" in the presence of congenital cardiac lesions in general, and isolated atrial septal defect in particular.[3, 5] In addition, patients with the clinical diagnosis of mitral stenosis made on the basis of classic criteria have been found to have only isolated atrial septal defect at surgery.[4] It therefore appears that many previous clinical studies on this syndrome may well have actually been dealing with the isolated atrial septal defect. This possibility is reflected in attitudes apparent in the recent literature, where investigators reporting cases of atrial septal defect, proved by catheterization, in which the patients had apical diastolic rumbles, have hesitated to make a definite diagnosis of Lutembacher's syndrome.[5, 6, 7, 8, 9] In the same situation, however, others have made a definite diagnosis.[10, 11] The data of Nadas and Alimurung [3] suggest that the diagnosis can be made only at autopsy or possibly at surgery.

Physiologic criteria for differentiating this syndrome from isolated atrial septal defect are not now available, since there are few data on this condition obtained ante mortem from cases verified at autopsy. This report is concerned with six cases of atrial septal defect with associated mitral valvular disease that were subjected to cardiac catheterization and verified at postmortem examination or during surgical repair of the atrial defect.

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FIG. 1. Chest film of case 1 taken at the time of cardiac catheterization in 1948.

CASE REPORTS

Case 1. A 23 year old woman was first seen in 1948 with a history of having had known heart disease as far back as her earliest recollection. She complained of a marked exertional dyspnea, palpitation, increasingly frequent cyanosis on exertion, and recently severe edema and swelling of the abdomen. She had been taking digitalis preparations continually for 15 years. There was no history suggestive of rheumatic fever.

Physical examination revealed an underdeveloped but moderately active patient. The blood pressure was 100/50 mm. of Hg. There was mild ankle edema. The heart was markedly enlarged. A systolic thrill was palpable along the left sternal border. A rough systolic murmur and a short, high-pitched diastolic murmur were heard over the base of the heart, in addition to an apical blowing systolic murmur and a low-pitched, mid-diastolic rumble.

Cardiac fluoroscopy revealed marked cardiac enlargement, predominantly right ventricular, with marked prominence of the pulmonary artery segment and its branches, and moderate left atrial enlargement (figure 1).

The electrocardiographic findings were consistent with right bundle branch block. The cardiac catheterization findings were consistent with septal defect (table 1).

The patient's course during seven periods of hospitalization was marked by progressive heart failure, with extreme ankle edema, increase in her exertional dyspnea and the appearance of an apical systolic thrill. Ascites became more marked, and there was development of subcutaneous edema. The patient went into progressive forward failure and died in 1952.

At post mortem the lungs were edematous; the right weighed 630 gm.; the left, 410 gm. The pericardial sac contained 150 c.c. of clear, straw-colored fluid. The heart weighed 890 gm., and dilatation of all chambers was noted. The left ventricular wall was 1.0 cm. thick; the right, 0.50 cm. The circumference of the tricuspid valve measured 18 cm.; pulmonary, 10 cm.; mitral, 11 cm.; aortic, 6 cm. The mitral valve opening was 4 cm. in diameter; its free edge and the chordae tendineae were thickened and covered with friable vegetations. The atrial septal defect measured

TABLE 1

Cardiac Catheterization

Case	Pressure, mm. of Hg				Oxygen Saturation, %						Blood Flow, l/min.	
	PA (mean)	RV	RA (mean)	*PV	PA	RV	RA	SVC	IVC	FA	Pulmonary	Systemic
1	34/16 25	33/3	3	—	87	85	62 (hi) 81 (lo)	52	—	94	27.9	3.8
2	35/10 18	28/7	7	—	89	90	81	56	—	96	11.0	2.2
3	43/21 31	71/9	6	6	87	—	87	65	—	91	22.3	4.26
4	82/37 53	78/17	20	21	87	84	86	61	75	93	12.1	3.53
5	53/16 30	55/12	—	—	87	—	85	57	69	93	21.2	4.65
6	39/17 18	57/10	—	—	89	—	92	58	—	95	18.8	3.65

* The catheter passed through an atrial septal defect into the left lung fields.

1.5 cm. in diameter. Tiny, nonfriable vegetations were present about the free margin (figure 2). The pulmonary arteries were moderately dilated, and atheromatous plaques were seen. The aorta was smaller than normal.

The final diagnosis was atrial septal defect, inactive mitral valvulitis and tricuspid insufficiency.

Case 2. A 48 year old woman was admitted to the medical service in 1952 with a two-year history of ankle edema, orthopnea and anterior chest pain. The patient denied having had rheumatic fever.

Physical examination revealed a well developed, tachypneic woman. The pulse was irregular; rate, 120/min. The blood pressure was 110/80 mm. of Hg. The apical impulse was palpable in the sixth intercostal space in the anterior axillary line. A coarse apical systolic murmur and a soft, blowing systolic murmur at the base were noted. No diastolic murmur was heard. The pulmonary second sound was accentuated. The liver was slightly enlarged and tender. There was moderate pitting edema of both ankles.

Cardiac fluoroscopy revealed a marked right ventricular enlargement with no definite evidence of left atrial enlargement. The pulmonary artery segment was prominent, and the pulmonary vascular markings were exaggerated, showing in-

creased pulsation (figure 3). An electrocardiogram revealed auricular fibrillation and right ventricular preponderance.

Following the routine management of congestive failure a cardiac catheterization was done (table 1).

Two weeks later repair of atrial septal defect was attempted, using hypothermia technic.[12] The defect was closed and the patient appeared to be doing well. The

FIG. 2. Photograph of the interatrial septal defect (above) in case 1, with thickening of the mitral valve and chordae tendineae below.

next morning, however, the heart rate was 40/min., and an electrocardiogram revealed a complete heart block. This condition persisted, with no evidence of pulmonary edema and no change in the minimal peripheral edema. The apical systolic murmur became less marked. On the third postoperative day the patient suddenly died without evidence of respiratory embarrassment.

On post mortem a thick layer of yellowish, fibrinous exudate covered the posterolateral surface of the right lung. The pericardial sac was open over the area of the right atrium and was everywhere else adherent. There was a 4 cm. surgical opening into the right atrium which was completely closed by sutures. The heart weighed 600 gm. All cardiac chambers were dilated, especially the right ventricle and right atrium. The left ventricle wall was 1.5 cm. thick and the right, 0.5 cm. The valve circumferences were as follows: tricuspid, 12.5 cm.; pulmonary, 9 cm.; mitral, 13.5 cm.; aortic, 6.5 cm. There was an atrial septal defect extending to the superior edge of the ventricular septum and measuring 2.5 by 4 cm. The cusps of the mitral valve were opaque and thickened with nodular edges (figure 4).

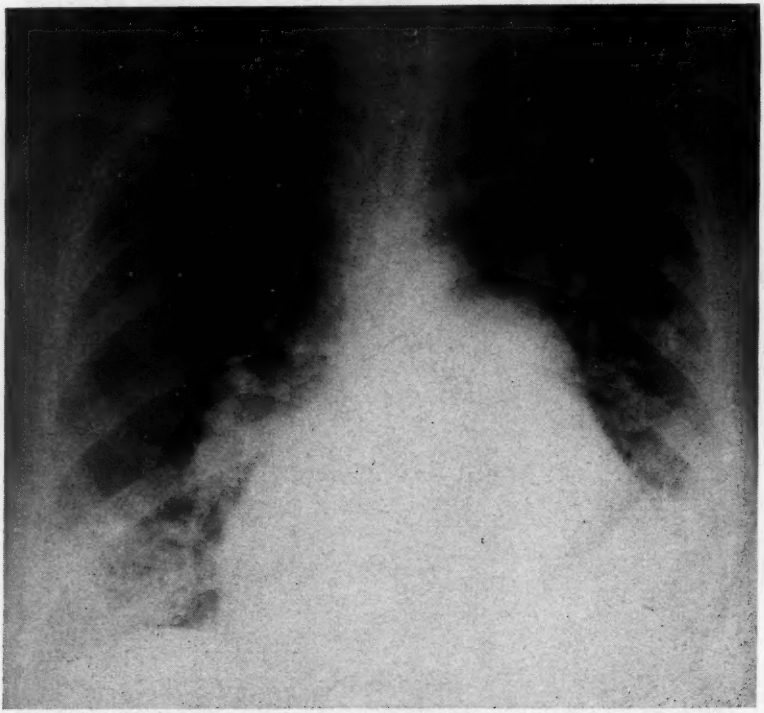

FIG. 3. Chest film of case 2 taken preoperatively.

Microscopic examination of a mitral valve cusp revealed it to be markedly thickened with abundant scar tissue. The nodular enlargements of its free edges consisted of swirls of hyaline scar tissue.

The final diagnosis of atrial septal defect with inactive mitral valvulitis was established.

Case 3. A 42 year old woman was admitted to the medical service with easy fatigability, mild exertional dyspnea and moderate ankle edema. At age 11 she had had a "mild attack" of rheumatic fever. At age 20, after a routine check-up, she was advised by her consultant to "take it easy," and restricted physical activities were im-

posed. Three years prior to her admission the diagnosis of mitral valve disease was made.

Physical examination revealed a well developed woman in no apparent distress. Blood pressure, 124/70 mm. of Hg; pulse, regular. A systolic thrill was palpable at the left sternal border (third to fourth intercostal space), and harsh systolic and blowing diastolic murmurs were heart at this area. Marked prominence of the second pulmonary sound was noted. The electrocardiogram was consistent with right ventricular preponderance. Cardiac fluoroscopy revealed a marked cardiac enlargement. The pulmonary artery segment and the peripheral lung vasculature were

FIG. 4. Photograph of the surgically closed interatrial septal defect above, with the thickened mitral valve below, in case 2.

prominent. Calcification in the wall of the left pulmonary artery was evident, and there was no definite enlargement of the left atrium.

Repair of the atrial septal defect was undertaken with the use of hypothermia technic. At surgery a high atrial septal defect was found, and exploration of the mitral valve revealed a stenotic mitral orifice which necessitated a mitral commissurotomy.

During the 22-month follow-up a tremendous physical improvement was noted, together with a decrease in the cardiac size, the disappearance of the previous recorded murmurs at the left sternal border and the subsequent appearance of a grade

I and II apical systolic murmur. One year following surgery, digitalis was discontinued.

Case 4. A 31 year old woman was said to have had a cardiac murmur in adolescence. Two years prior to her admission she aborted a two month fetus and began complaining of pain in the right upper quadrant of the abdomen, exertional dyspnea, palpitation, chills and fever. She was admitted to a local hospital with the diagnosis of rheumatic fever. One year later a mitral commissurotomy was attempted but an atrial septal defect was found at surgery. Subsequently she was maintained on digitalis, mercurial diuretics, bed-rest and a low salt diet.

On admission her pulse was irregular, the neck veins were distended, and a precordial bulge was observed. The heart was enlarged. A systolic thrill was palpable over the precordium, a soft blowing systolic and a diastolic rumble were heard at the apex; a harsh systolic murmur together with an accentuated second sound was noted at the pulmonic area. The liver edge was palpable three fingerbreadths below the right costal margin and was slightly tender.

The electrocardiogram revealed auricular flutter with a ventricular rate of 75/min., plus a right bundle branch block.

Cardiac fluoroscopy revealed a massive heart, mainly due to right ventricular enlargement. Prominent pulmonary artery segment, peripheral lung vessels and marked pulsation of the major pulmonary vessel were noted, together with left atrial enlargement.

Following cardiac catheterization (table 1), a repair of the atrial defect together with dilatation of the mitral valve was done under hypothermia. At surgery a large defect of the atrial septum (septum secundum) was found, measuring 4.5 to 5.0 cm. at its greatest dimensions, just above the inferior vena cava opening. Further exploration revealed a normal tricuspid valve and a pathologic mitral valve; its aortic leaf was soft, and the mitral orifice seemed to be crossed with bands of tissue, the largest opening barely admitting a fingertip. A jet during ventricular systole was felt in the left atrium.

Following surgery congestive heart failure persisted. A soft blowing apical systolic murmur and a probable apical diastolic rumble were present. A repeat of the cardiac catheterization established the completeness of the atrial repair, but no change in cardiac fluoroscopy findings was evident.

Case 5. A 26 year old woman was admitted to the medical service with complaint of precordial fullness. At age 12, during a routine physical examination, a heart murmur had been discovered. Two years prior to admission she developed pneumonia and later was digitalized, and since had been maintained on digitalis. She had had one episode of right hemiparesis several years previously that had lasted a few days. The patient was referred to the hospital with the diagnosis of mitral stenosis.

Physical examination revealed a well developed female. The pulse was irregular, the rate was 80/min., and a blood pressure was 112/76 mm. of Hg. Soft blowing apical systolic and diastolic murmurs were heard. The pulmonic second sound was split. The heart was slightly enlarged. No ankle edema was noted.

Cardiac fluoroscopy showed a marked generalized cardiomegaly. The left atrium, the pulmonary artery segment and peripheral vascular markings were especially prominent.

The electrocardiogram revealed auricular fibrillation with a slow ventricular rate and a right bundle branch block.

Cardiac catheterization was done (table 1) and the findings were consistent with an atrial septal defect, which had not been suggested by the clinical findings.

At surgery a repair of a septum secundum, 2.5 cm. in diameter, was done. The

tricuspid valve was normal and the mitral orifice was stenosed, barely admitting the tip of the finger. A mitral commissurotomy was done.

Follow-up over a period of two and one-half years showed a slight decrease in cardiac size, the disappearance of the apical diastolic murmur and marked functional improvement.

Case 6. The patient was an 18 year old girl who was referred to the medical service with complaints of easy fatigability and mild dyspnea on exertion. She had known of the presence of a heart murmur from early childhood, but denied a history of rheumatic fever.

Physical examination revealed a well developed girl with a rough systolic murmur located at the third to fourth left (parasternal) intercostal space, and associated with a systolic thrill. A mid-diastolic rumble was also heard at the apex of the heart. On cardiac fluoroscopy there was extreme enlargement of the heart, chiefly right ventricular, with a prominent pulmonary segment and pulmonary vasculature. An electrocardiogram revealed a normal sinus rhythm and was consistent with right ventricular preponderance. Cardiac catheterization data (table 1) were consistent with an atrial septal defect.

At operation the mitral valve was stenosed, admitting only the tip of the index finger. This was enlarged to admit approximately two fingers. The atrial septal defect of the septum secundum type was repaired at the same time.

A postoperative cardiac catheterization revealed a complete closure of the defect. The cardiac murmur previously heard disappeared following surgery.

Catheterization Findings

The left-to-right shunt exceeded by far the systemic blood flow (table 1). It should be pointed out that these values for the shunt cannot be considered highly accurate, and that they indicate only an order of magnitude: first, the pulmonary artery-femoral artery oxygen contents are so similar that the A-V oxygen difference is very small, giving a large value for pulmonary blood flow; second, the systemic blood flow (in case the inferior vena cava was not catheterized) is calculated partially from the superior vena cava oxygen content, which is taken to represent the mixed venous sample but in reality is not a mixed venous sample.

The femoral artery saturation (cases 1, 3, 4 and 5) indicates the presence of a small right-to-left shunt. This finding does occur in uncomplicated atrial septal defect, but may also appear in the presence of mitral stenosis.

The finding of a comparatively higher systolic pressure in the right ventricle than in the pulmonary artery (cases 3 and 6) does not necessarily indicate the presence of a mild pulmonary stenosis. In our experience there was such a finding in a number of patients with an increase in the pulmonary blood flow but it was not present when the pulmonary blood flow returned to normal.

Discussion

An examination of the data, both clinical and laboratory, obtained in these proved instances of mitral valvular disease with atrial septal defect indicates that it is, for practical purposes, impossible to differentiate the ordinary case of this syndrome from simple atrial septal defect. Cardiac

fluoroscopy, murmurs, electrocardiogram and the physiologic data in these proved instances of Lutembacher's syndrome are in no way different from similar observations in proved instances of isolated atrial septal defect.

The present data on pressures, oxygen saturations, the calculated left-to-right shunts and the cardiac outputs fall well within the range of values previously observed in patients with isolated atrial septal defects.[6, 7, 10, 11] It is therefore unlikely that physiologic data of any one case of atrial septal defect associated with mitral lesion could be helpful in differentiating it from the isolated atrial septal defect.

Clinically, the differentiation of the two conditions is also difficult. The typical murmurs of mitral disease may be present in purely congenital lesion in the absence of mitral involvement.[3, 5] Furthermore, true mitral murmurs in the presence of a mitral lesion may be minimal or even lacking, as noted in cases 2 and 3.

Differentiation of the two conditions could not be made by radiographic studies of the heart and the pulmonary vasculature. In cases 4 and 5 these findings were indistinguishable from those of a simple mitral valve disease. Case 4 had a cardiotomy before the diagnosis was established, and in case 5 the cardiac catheterization was done before surgery was attempted for mitral commissurotomy. A marked cardiac enlargement and prominent pulmonary vessels have been said to differentiate the two conditions.[1, 2] However, such changes can be seen in an isolated atrial septal defect with a large left-to-right shunt, since increase in size of the heart and pulmonary vessels is probably related to the amount of pulmonary blood flow.

There are probably only two circumstances under which the diagnosis can be made clinically, short of cardiotomy or autopsy. If calcification of the mitral valve can be observed radiographically in the presence of a proved atrial septal defect, the diagnosis of Lutembacher's syndrome would seem to be well founded. In the absence of calcium, however, the only other way to make the diagnosis would be to measure a gradient across a stenosed mitral valve, either by introducing a catheter through the atrial septal defect and into the left atrium and left ventricle, or by direct left atrial puncture, and then introduction of the catheter into the left ventricle. If a significant gradient could be demonstrated across a stenosed mitral valve under these circumstances, the diagnosis of Lutembacher's syndrome would certainly seem to be well grounded.

The experience with the group of cases herein reported would indicate that, for practical purposes, a clinical diagnosis of combined atrial septal defect and mitral valvular disease can never be made with certainty, and for that reason many of the instances reported in the literature in which there is neither operative nor autopsy confirmation must be questioned. The fact that six cases have been proved out of a total operative series of 63 adults with atrial septal defects suggests that the incidence of the combined lesion is in accordance with the previous report.[2]

As far as treatment is concerned, it has been proved reasonable first to do a mitral valvotomy through the atrial septal defect, then to repair the defect, provided the mitral valvular lesion is predominantly stenosis. If the predominant valvular lesion is mitral insufficiency, there is serious question as to whether repair of the atrial septal defect should be undertaken, since it is conceivable that the shunting of blood from left atrium to right atrium might be a highly effective method for sparing the lesser circulation and preventing the occurrence of irreversible changes in the small pulmonary vessels that may accompany mitral insufficiency. In case 5, in whom marked mitral insufficiency was surgically produced, a marked increase in pulmonary artery pressure was observed postoperatively, as well as a marked increase in the right ventricle systolic work.[13] For these reasons an accurate preoperative differential diagnosis would be highly desirable, but it seems as of now not to be possible.

Summary

Six cases of atrial septal defect associated with mitral valvular disease are presented. These cases were proved either at cardiotomy or at autopsy. The total unreliability of the cardiac murmurs in this situation and of clinical and laboratory data to differentiate the combined lesion from simple atrial septal defect has been emphasized. There appear to be at this time no adequate criteria for making a differential diagnosis between these two conditions, short of measuring a gradient across a stenosed mitral valve in a proved case of atrial septal defect, or short of demonstration of mitral valvular calcification in a patient with proved atrial septal defect. It would appear that this combination of lesions is relatively common, occurring in about 10% of operative cases of atrial septal defect.

Summario in Interlingua

Esseva studiate sex patientes adulte con defecto atrio-septal e morbo del valvula mitral. Le criterios jam establite pro le diagnose de iste combination es passate in revista e discutite. Il ha essite monstrate que le aspectos clinic e le constatationes roentgenographic in tal patientes non suffice pro differentiar le combinate lesion cardiac ab le simple e non-complicate defecto atrio-septal. In le casos del presente serie, diastolic tonos rolante al apice non esseva presente uniformemente. Le signification diagnostic de tal tonos es dubitose in le presentia de congenite lesiones cardiac, specialmente de defectos atrio-septal. Studios physiologic de iste patientes per medio de catheterisation cardiac non succedeva melio a differentiar le lesion combinate ab le non-complicate defecto atrio-septal.

Durante le vita del patiente (e sin considerar intervention chirurgic), le diagnose del associate lesion mitral esseva possibile in casos in que calcification del valvula mitral esseva demonstrabile roentgenographicamente. Es mentionate le possibilitate de passar un catheter cardiac ab le atrio sinistre a in le ventriculo sinistre con le objectivo de demonstrar le existentia de un gradiente de signification diagnostic.

Alteremente le differentiation del duo conditiones—non-complicate defecto atrio-septal e defecto atrio-septal combinate con morbo del valvula mitral—esseva possibile solmente in le intervention chirurgic o al necropsia.

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A REVIEW OF WERNER'S SYNDROME, WITH A REPORT OF THE SECOND AUTOPSIED CASE*

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In 1868 Rothmund [1] published his observations on "Cataracts in Association with a Peculiar Degeneration of the Skin," a heredofamilial disorder found in the consanguineous populations of three small Bavarian villages. Thirty-six years later another German ophthalmologist, Werner,[2] independently described an odd syndrome entitled "Cataract in Connection with Scleroderma," involving two sisters in a family of six siblings.

Further observations were not published until material from German and French sources appeared in the 1920's. However, no distinction between these two syndromes was made until the first report in the American medical literature in 1934, when Oppenheimer and Kugel [3] distinguished the conditions described by Werner and Rothmund and established the eponym now known as Werner's syndrome. The disease, occurring with equal frequency in male and female, usually becomes manifest in the decade after adolescence, when hitherto normal development is altered by graying of the hair, impairment of normal growth, loss of the subcutaneous tissue and muscle mass of the extremities, and progressive changes in the skin of the hands and especially the feet, with gradually diminishing proximal severity. The limbs become slender, and the trunk becomes disproportionately stocky. The shiny atrophic hyperkeratotic skin, unpadded by subcutaneous fat, is pulled so tightly over the bony prominences that arthrogryposis develops. Painful, circumscribed callosities occur, especially on the soles, and indolent ulcers appear at pressure points (malleoli of ankles, Achilles tendon, heels and toes). Baldness appears, and the hair thins over eyebrows, face, axillae and pubis. The physiognomy is often characteristically altered as the taut skin of the cheeks causes beaking of the nose, as shallow orbits and loss of periorbital connective tissue produce the appearance of proptosis, and as thick-lensed glasses are needed after extraction of rapidly progressing cataracts. The peculiar thickening and vascularity of vocal cords is associated with a weak, high-pitched voice. Arteriosclerosis is strikingly premature, and sexual underdevelopment results in varying degrees of impotence and sterility.

Diabetes is frequent. Areas of calcification occur in the skin and subcutaneous tissue (calcinosis circumscripta). The skeleton is frequently

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affected by osteoporosis and hypertrophic arthritis. The fully developed syndrome creates a remarkably constant picture of premature senility, short stature, spindly extremities, stocky trunk, and beak-nosed, bespectacled facies. Siblings are often similarly affected, and isolated manifestations, the "forme fruste," such as canities or cataracts, are commonly found sporadically in other members of the family.

In an excellent review article Thannhauser [4] distinguished the skin changes in Werner's syndrome from those of scleroderma, reëmphasized the differences between Werner's and Rothmund's syndromes, and discussed four other distinct but apparently related disorders: *cataracta dermatogenes, hereditary ectodermal dysplasia, dystrophia myotonica* and *progeria of children with nanism* (the Hutchinson-Gilford syndrome).

Rothmund's syndrome is a heredofamilial disease beginning a few months to a few years after birth, principally involving the skin of the face, ears, cheeks and buttocks, followed by rapidly developing bilateral cataracts, little or no retardation of growth, and only mild deficit of sexual development. The skin, though thin, atrophic and scaling, does not become taut. Telangiectases are pronounced, and there are areas of pigmentation and depigmentation. Ulcers are conspicuously absent. Atrophy of muscle and subcutaneous fat, premature arteriosclerosis, osteoporosis, proptosis and canities are either absent or insignificant.

In 1886 Vidal [5] described a chronic dermatitis which tended to occur in young, emotionally labile patients, and which was characterized by pruritus, thickening of the skin, lichenification, fall and winter exacerbations associated with asthma, and a predilection for flexor surfaces, popliteal and antecubital fossae, face, forehead and neck. Twenty-five years later, Andogsky [6] reported the presence of bilateral cataracts in a 15 year old youth with chronic dermatitis. To this he attached the name *cataracta dermatogenes,* or "neurodermatitis with cataract." Cortical subcapsular opacities, which may be either unilateral or bilateral, characteristically begin suddenly from one to 19 years after the onset of early childhood eczema,[7] and may proceed to complete maturity within a few weeks. The evidence for hereditary transmission is unconvincing, although it is not uncommon to find isolated cases of allergy, eczema or asthma in the family history. The presence of cataracts with this cutaneous disorder is relatively infrequent, varying from 2 to 20%.[8] It appears, therefore, that the picture of Werner's syndrome is distinct from cataracta dermatogenes.

Weech [9] in 1929 used the term *anhydrotic ectodermal dysplasia* to describe a rare hereditary disorder occurring predominantly in males, characterized by absent lanugo, sparse, dry, brittle scalp hair (hypotrichosis), abnormalities of dentition (oligodontia or anodontia), diminished sebaceous activity, and an inability to sweat (anhydrosis). There may be associated atrophy of upper respiratory mucous membranes, diminished lacrimation, absent mammary glands, ageusia, anosmia and mental retardation. McKay and Davidson [10] described an apparent variant of this syndrome in which

sebaceous and sweat glands are intact, but changes in skin, hair and nails develop shortly after birth. The head becomes bald, and hyperkeratosis appears on the palmar and plantar skin. These anomalies are distinguished from Werner's syndrome, however, by being exclusively ectodermal defects which occur without cataracts or presenility.[11]

Initial interest in *dystrophia myotonica,* clearly a familial disorder,[38] was directed toward the striking alterations in skeletal muscle. Myotonia (slow relaxation after contraction), occurring especially in hand and forearm after voluntary or mechanical stimulation, is associated with muscle atrophy of typical distribution. Wasting of the temporalis, orbicularis oculi and orbicularis oris results in the typical, expressionless "myopathic facies." The sternocleidomastoid often becomes severely atrophic, and involvement of pharyngeal groups may result in a low-pitched, nasal voice. Though any striated muscle can be affected, the other frequently involved groups are those of the hands, forearms, quadriceps and dorsiflexors of the feet. Microscopic changes in skeletal muscle [36, 37] are described as inward migration of nuclei to form typical centrally placed rows (a constant histopathologic finding), transverse cleavage of fibers by inward growth of connective tissue and capillaries, thick peripheral layers of sarcoplasm, striated fibrillar rings (striated annulets or Ringbinden of Heidenhain), and ultimate atrophy with connective tissue replacement. Clinical evidence of cardiac involvement is not uncommonly noted. Hypotension, bradycardia, distant heart sounds, cardiac enlargement, atrial arrhythmias, congestive failure, and a high frequency of abnormal electrocardiograms,[13] especially conduction defects, seem well established. Adams, Denny-Brown and Pearson [37] state that the cardiac muscle does not show the changes present in peripheral skeletal muscle, and Wohlfart,[36] in a histopathologic study of 19 cases, failed to mention abnormalities of cardiac muscle. However, Black and Ravin [12] described atrophy, variability in size of fibers, and variation in nuclear size and shape, and more recently Fisch [14] reported finding normal coronary arteries associated with diffuse myocardial fibrosis, separation of fibers by fibrous connective tissue, and scattered hypertrophied fibers with large nuclei.

Cataracts, which may precede the muscle changes, are frequent, as are frontal baldness, testicular atrophy (seminiferous tubular degeneration), infertility, menstrual irregularities, and what appears to be extrathyroidal hypometabolism.[38, 39] The endocrine glands have understandably been incriminated, but in spite of scattered pathologic evidence of changes in anterior pituitary, adrenal cortex, thyroid and thymus, there is no well established histopathology of ductless glands in myotonic dystrophy. Recent metabolic studies [38, 39] have revealed normally functioning pituitary, adrenal cortex, thyroid and parathyroid, and Leydig's cells which responded to chorionic gonadotropin. Reports of carbohydrate intolerance are conflicting. Rymer and Ravin,[15] in a small but careful study, found no abnormality of islet tissue, though three of the eight cases of Jacobsen, Schultz and Anderson [39] had diabetes, and Caughey and Brown [40] found impaired glucose tolerance in two

more patients. It is suggested that the incidence of abnormal carbohydrate metabolism may be greater in myotonic dystrophy than in the general population.

Dystrophia myotonica might therefore be considered a systemic disease, the most dramatic facet of which is the disorder of skeletal muscle. The parallels between many of its features and those of Werner's syndrome are of interest.

The syndrome of *progeria with nanism* was originally described by Hutchinson in 1886, and 18 years later was appropriately named *pro* (before) *geras* (old age) by Gilford.[18] Of the 23 reported cases, 10 were female and 13 male. After a normal birth and infancy the disorder becomes evident about the first year of life, classically manifesting itself as dwarfism, alopecia (usually totalis), a protuberant, thick-skinned abdomen, disproportionately short legs, atrophic, taut skin, loss of subcutaneous fat, micrognathios, small clavicles, coxa valga, prominent scalp veins, senile appearance with premature arteriosclerosis, hypertrophic arthritis, and normal intelligence. Early death from myocardial infarction is not uncommon. Though progeria is considered to be nonhereditary, Garbr [19] noted that in one case the mother had alopecia and in another the father had micrognathios, and in four cases cleidocranial dysostosis (said to be heredofamilial) was present. In an additional case of his own, a sister had alopecia, abnormal skin and coxa valga.

In five postmortem studies [18, 19, 20, 21] the findings failed to clarify the clinical picture. Etiology is obscure. The repeated contention that the condition is primarily an endocrinopathy is unsupported by these autopsies. In his studies of a case prior to post mortem, Talbot [20] felt that a fundamental part of the disorder was an excessive basal energy metabolism, not due to hyperthyroidism. Hence, in spite of adequate dietary intake and absorption, the hypermetabolic state, by completely utilizing the energy derived from food, left nothing available for growth and development. What might initiate such an energy state is not speculated upon. The disease no more than superficially resembles hereditary ectodermal dysplasia but, except for the absence of cutaneous ulcers, cataracts, and clear familial occurrence, it has many features in common with Werner's syndrome. Indeed Thannhauser [4] suggested that the two disorders might be basically similar defects manifesting themselves at different ages.

The following material is from a classic case of Werner's syndrome which came to autopsy after several years of clinical observation. Except for Oppenheimer and Kugel's study, published 15 years ago, there are no other known postmortem data. Because of this, and because of the rarity of the disorder, we felt that a report of our observations was warranted.

Case Report

History: The patient, a white male, first entered Georgetown University Hospital in August 1953 at the age of 47. His birth, infancy and early childhood had been

normal, but he is said to have been underweight and undersized since adolescence. Tight, dry skin, especially of the lower extremities, was noted at the age of 11 or 12 years, and callosities of the soles appeared in sequence. At the age of 30 the first of recurrent, indolent ulcers became manifest on the malleoli and Achilles tendons. Three years later rapidly progressive bilateral cataracts appeared, and the following year, at the age of 34, loss of potentia coeundi occurred, with initial retention of libido. At the same time baldness began, with canities and a decrease in axillary, pubic and facial hair. Shortly thereafter the pitch of the voice slowly became higher and its strength diminished. About the latter part of his fourth decade the patient began to drink progressively larger amounts of alcohol to relieve the pain of the ulcers. At approximately this time he was admitted to the District of Columbia General Hospital, where the diagnosis of Werner's syndrome was established. Two years later he began a series of re-admissions to that hospital for bilateral cataract extractions, bilateral lumbar sympathectomies, skin grafts at the site of indolent ulcerations, and finally, in 1953, at the age of 47 years, for a Smith-Bennett midleg amputation. There was, in addition, an admission in 1951 for right upper lobe pneumonia and melena, following which the patient stopped drinking alcohol. Because of the progressive disability, further care was arranged in the Washington Home for Incurables, from which subsequent admissions were to Georgetown University Hospital.

Two months prior to the initial admission to this hospital the patient had what descriptively was an acute myocardial infarction, followed by dyspnea, mild orthopnea, and recurrent pain of myocardial ischemia.

Family History: The parents were second cousins. The mother, who died of puerperal sepsis at the age of 30 years, was said to have had leg ulcers. The father, who remarried, is now 79 years old and is said to be in good health except for heart disease. The first marriage resulted in seven siblings, of whom the patient was the youngest. Two died in infancy. Two brothers, ages 52 and 56, are living and well. The younger sister, age 48, is being followed at the Johns Hopkins Hospital. Her symptoms began at age 20 with callosities of the soles, and gradually progressed to include the typical taut, shiny, dry, atrophic skin of the face, lower legs, ankles and feet, recurrent indolent distal leg ulcers, especially on malleoli and Achilles tendons, soft tissue calcification about the right ankle, and bilateral cataracts which on slit lamp examinations were described as peripheral cortical and posterior subcapsular. This patient has undergone bilateral lumbar sympathectomies, successful skin grafts of leg ulcers, and finally bilateral leg amputations as well as extraction of the cataracts. The elder sister, age 55, married but childless, is being followed for a virtually identical problem at the University of Virginia Hospital. Thus far she has had bilateral extraction of cataracts which began at age 36, and successful skin grafts of malleolar ulcerations.

Marital History: The patient had a childless marriage between the ages of 26 and 32, ending in separation.

Physical Examination on First Admission: The patient presented as a small (5′ 5″), poorly developed, somewhat cachectic individual who appeared about 15 years older than his stated age of 47, and who responded in a weak, high-pitched voice. The head was covered by a thin, peripheral rim of gray hair, and there was axillary, pubic and facial hypotrichosis. The face was characteristically altered by moderate micrognathios, thin, taut malar and perioral skin, and mild proptosis emphasized by the thick spectacles worn since the cataract extractions. The right leg was amputated below the knee. The cutaneous lesions were most marked in the distal portion of the remaining leg, less marked in the hands and arms, with gradually decreasing proximal severity, so that the upper arms, thighs and trunk appeared remarkable only because of their senile consistency. Shiny, smooth, atrophic, scaly skin was drawn so tightly over the prominences of the foot that motion of several toes was

limited and peripheral pulses could not be felt. Limb muscles were atrophic, profoundly so, peripherally. A small ulcer was present on the left heel. Advanced changes of hypertrophic arthritis involved both hands. The lungs were clear. The blood pressure was 100/60 mm. of Hg in the right arm and 106/70 mm. of Hg in the left arm. The pulse was 80 per minute, the rhythm regular. There was no jugular venous distention. The heart was equivocally enlarged to the left. There was a grade 3 aortic systolic murmur which was heard with diminished intensity at the apex. The second sound in the pulmonary area was single and greater than the second sound in the aortic area. A faint apical protodiastolic gallop was variably heard. A sharp, nontender liver edge was felt 3 cm. below the costal margin. The penis was reduced in size; the testes were firm and small.

Laboratory Findings: Urine: Specific gravity, 1.011 to 1.022; pH, 5.5; albumin, 0 to 1 plus; sugar, negative. Microscopic examination revealed occasional white blood cells and an occasional granular cast.

Blood: Hematocrit, 29%; red blood cell count, 3,660,000 per cubic millimeter; hemoglobin, 9.8 gm.%; mean corpuscular volume, 79 cubic microns; mean corpuscular hemoglobin, 26.5 micro-micrograms; mean corpuscular hemoglobin concentration, 33.8%. The white blood cell count and differential count were normal. Total eosinophil count, 345 per cubic millimeter. Corrected erythrocyte sedimentation rate, 17 mm./hour (Wintrobe). Platelets, 234,000 per cubic millimeter. Bone marrow was hypercellular, with moderate relative increase in basophilic rubricytes, consistent with chronic iron deficiency anemia.

Blood Chemical Studies: Calcium, 10.2 to 10.3 mg. per 100 ml.; phosphorus, 3.5 to 4 mg. per 100 ml.; alkaline phosphatase, 11.9 to 17.8 Bodansky units; bromsulfalein, 10% retention in 45 minutes; albumin/globulin fractionation, 4.5/3.6; total cholesterol, 299 mg. per 100 ml.; cephalin flocculation, negative in 24 and 48 hours; thymol turbidity, 6 Maclagan's units; blood urea nitrogen, 13 mg. per 100 ml.; phenolsulfonphthalein: 15 minute excretion, 35%; 30 minutes, 10%; 60 minutes, 30%; 120 minutes, 25%; 24-hour urinary excretion of 17 ketosteroids (volume, 1,250 c.c.), 6.2 mg.; iodine 131 uptake, 24% (normal, 10 to 45%); stool guaiac, repeatedly negative; serologic test for syphilis, negative; glucose tolerance: fasting blood sugar, 108 mg. per 100 ml.; one-half hour, 260; one hour, 224; two hours, 184; three hours, 136; four hours, 80.

Electrocardiogram: Healed diaphragmatic wall myocardial infarction.

X-rays: Chest: normal heart with calcium in the aortic arch and fibrocalcific lesion at the apex of the right lung. Upper gastrointestinal series and barium enema with air contrast were normal. Marked calcification of the splenic artery was incidentally noted. Skull: normal except for marked calcification of the internal carotid artery. Cervical spine: degenerative arthritis, C3 and C4. Left lower extremity: marked osteoporosis, bone resorption of the proximal phalanx of the small toe and the head of the fifth metatarsal, soft tissue calcification anterior to the patella. Right lower extremity stump: periosteal reaction along the lateral portion of the tibia, with osteoporosis of the remaining bone structures. Right elbow: soft tissue calcification of the posterior aspect of the elbow.

Treatment: The patient was fully digitalized with the whole leaf, given nitroglycerin, to which he responded well, and discharged on oral ferrous sulfate, maintenance digitalis, and a low sodium diet. He had symptomatically improved.

Second Admission: The second admission was seven months later. After a relatively stable interval, typical exertional angina had begun three months prior to admission. Three weeks before admission the patient developed anorexia, a seven pound weight loss, and a cough productive of yellowish white mucoid sputum. He had taken the above medications irregularly. When seen, the oral temperature was 100° F., and there were signs of pleural effusion. Diagnostic thoracentesis yielded

500 c.c. of slightly cloudy yellow fluid which coagulated upon standing. The specific gravity was 1.014; 1,707 cells (600 white blood cells); Gram's and Ziehl-Neelsen stains were negative for bacteria. Routine and acid-fast cultures were negative. Cell block revealed no malignant cells. Sputum grew *Diplococcus pneumoniae* and a few colonies of alpha hemolytic streptococcus and *Neisseria catarrhalis*. Smear and culture of sputum for tuberculosis were negative. Electrocardiogram revealed anterolateral subendocardial ischemia. Blood: white cell count, 10,000 per cubic millimeter, 68 segmented neutrophils, 24 lymphocytes, 5 monocytes and 3 eosinophils. Hematocrit, 32%; red blood cells, 4,030,000 per cubic millimeter; hemoglobin, 9.8 gm.%; reticulocytes, 3.4%. Stools were guaiac-negative. The patient was given 2 gm. of Terramycin daily and was transfused with two units of packed red blood cells. The pulmonary lesion slowly cleared and the hematocrit rose to 41.5%. The patient was discharged on digitalis leaf, salt restriction, nitroglycerin and ferrous sulfate.

Third Admission: The third admission was eight months later, for surgical removal of the capsule of the right lens. The admission urine disclosed 4 plus glycosuria. The fasting blood sugar was 93 mg.%; the two hour postprandial blood sugar was 325 mg.%. The patient was transferred to the medical service. Laboratory studies there revealed a urine specific gravity of 1.022; pH, 4.5; sugar, 3 plus; acetone, negative; microscopic examination, negative. Blood urea nitrogen, 20 mg. per 100 ml.; bromsulfalein, 8% retention of dye in 45 minutes; cholesterol, 235 mg. per 100 ml.; stool, guaiac-negative; hematocrit, 45%; hemoglobin, 15 gm.%. Glucose tolerance curve: fasting blood sugar, 93 mg. per 100 ml.; 15 minutes, 210; 30 minutes, 268; one hour, 375; two hours, 370; three hours, 230; four hours, 90, with glycosuria 0 to 4 plus. Chest x-ray revealed the heart and lungs to be within normal limits. Carbohydrate intolerance was controlled on an 1,800 calorie American Diabetic Association diet.

Fourth Admission: Eight months after discharge the patient returned for his final admission, with a four-week history of progressive dyspnea, orthopnea, marked asthenia, fatigue, a 10- to 15-pound weight loss, and frequent constricting precordial pain occurring at rest and inconstantly relieved by nitroglycerin. The admission blood pressure was 90/60 mm. of Hg; pulse, 90 per minute, the rhythm regular with a pulsus alternans. The patient presented as a markedly cachectic, emaciated, aged man, dyspneic, orthopneic and profoundly weak. In addition to the aortic systolic murmur, there was a pansystolic apical murmur of relative mitral incompetence with a protodiastolic gallop. The apex beat was 1 cm. beyond the midclavicular line. The lungs were clear. The liver was still 2 to 3 cm. below the costal margin.

Laboratory Findings:

Urine: Albumin, trace to 3 plus; sugar, trace; acetone, 0; microscopic: two to eight white blood cells and four to five red blood cells per high power field; urine culture, sterile.

Blood: Hematocrit, 38%; hemoglobin, 13 gm.%; corrected erythrocyte sedimentation rate, 30 mm./hour; white blood cell count, 10,650 per cubic millimeter, with a normal differential count. Total eosinophil count, 200 per cubic millimeter.

Chemical Studies: Fasting blood sugar, 90 mg. per 100 ml.; CO_2 content, 22.5 mEq./L.; chloride, 97 mEq./L.; sodium, 144 mEq./L.; potassium, 4.5 mEq./L.; alkaline phosphatase, 5 Bodansky units; albumin/globulin ratio, 3.6/3.9.

Biopsy of skin from extensor surface of right forearm: see pathology report.

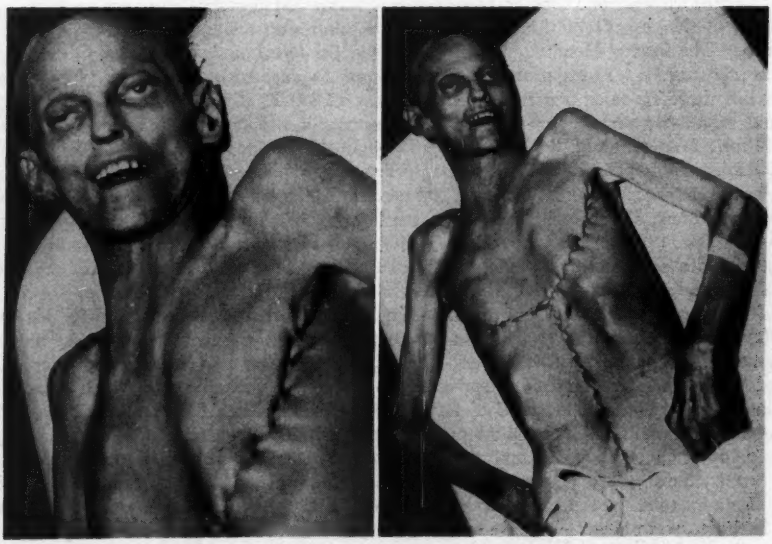
The *electrocardiogram* was similar to that taken on the second admission. The immediate suggestion of hypo-adrenocorticism or hyponatremia induced by mercurial diuretics and sodium restriction was resolved by the initial laboratory results. The extreme cachexia and rapid deterioration strongly suggested a malignant neoplasm. However, the patient was too ill to tolerate investigation, and was found dead in bed on the fifth day after admission.

Autopsy Observations:

(For the sake of brevity, only summary data will be recorded in the following protocol. The postmortem examination was performed 16 hours after death.)

The body was substantially as indicated by the clinical description (figure 1).

Heart: Weight, 450 gm. The right auricle was dilated. Both ventricles appeared somewhat hypertrophied: the left was 1.5 cm. in thickness, the right, 8 mm. In the apex of the left ventricle there was an area of fibrosis in which calcium was deposited. Section revealed scattered areas of fibrosis in the walls of both ventricles. The aortic orifice measured 6 cm. in circumference. There was advanced calcification involving the sinuses of Valsalva, the aortic ring and the cusps, which had become adherent. The coronary ostia were small. The coronary arteries were intermittently narrowed by arteriosclerotic plaques, none of which completely occluded a lumen.



A B

FIG. 1. Postmortem photographs illustrating (A) the profound cachexia, the frontal baldness, and the sunken orbits with apparent proptosis, and (B) relatively severe involvement of the skin of the distal portions of the upper extremities. Tape is at site of forearm biopsy.

Aorta and great vessels: The carotids were markedly arteriosclerotic, often to the point of brittle rigidity. There was remarkable atherosclerosis of the descending, thoracic, and especially the abdominal aorta. The calcified splenic artery was reduced to a tortuous, rigid tube.

Lungs: The right lung weighed 560 gm., the left, 520 gm. There were about 100 c.c. of straw-colored pleural fluid bilaterally. Scattered pleural adhesions were present in both cavities. In the apex of the right lower lobe there was a 1.5 cm. caseous focus in which calcium was deposited.

Liver: Weight, 1,320 gm. Grossly unremarkable.

Kidneys: The left kidney weighed 150 gm., the right, 130 gm. The capsules stripped easily. The organs, including cut surfaces, were grossly unremarkable.

Spleen: Weight, 220 gm. Grossly unremarkable.

Testes: Reduced in size. The tubules did not string well from the cut surface.

Brain: The frontal lobes were reduced in size. The arteries at the base of the brain were remarkable because of their brittle, arteriosclerotic rigidity.

Microscopic Protocol:

Heart: The following is a composite of multiple areas of both ventricles. The epicardium was covered by normal mesothelium, beneath which the connective tissue was somewhat increased. There were scattered lymphocytes in the subepicardial fat. In the myocardium there were occasional areas in which fibers appeared hypertrophied. Lipochrome granules were frequently found at the poles of nuclei. There were many scattered foci of varying size in which muscle had been replaced by fibrous connective tissue. In the section taken from near the apex of the left ventricle, there was a similar but much larger area which was heavily calcified from epicardium to endocardium. The intramyocardial blood vessels appeared normal. Most sections revealed significant subendocardial sclerosis.

Aorta: Multiple sections revealed advanced arteriosclerosis.

Lung: The bronchioles were unremarkable. The alveoli varied considerably in size, some coalescing to form emphysematous air sacs. Many alveolar spaces contained pigment-laden macrophages. Throughout the sections, most of the alveolar walls revealed a slight degree of membranous thickening just beneath the epithelial lining of the alveolar space. The arterioles generally revealed a moderate degree of medial fibrohyaline thickening. The venous channels appeared normal except for increase in adventitial connective tissue. There was one large fibrous encapsulated area of caseous necrosis surrounded by a thin layer of mononuclear cells. A few small tubercles with multinucleated giant cells were in the vicinity.

Liver: The normal architecture was preserved. The parenchymal cells around the central veins were shrunken and poorly stained, exaggerating the prominence of the reticular framework in this area. In some areas the nuclei appeared to be undergoing vacuolar swelling. Many cells contained fat vacuoles in the cytoplasm. Scattered irregularly throughout the section were numerous round, deeply eosinophilic-staining bodies of varying size containing round, solid, dark-staining central masses. There was increase in fibrous connective tissue in some portal areas.

Gall-bladder: The mucosa was completely autolyzed. In the muscularis, some of the larger blood vessels revealed moderate medial thickening and an increased amount of adventitial connective tissue.

Spleen: The capsule was thick and fibrous. Periodic acid stains revealed a somewhat prominent reticulum extending from beneath its surface deep into the splenic pulp, which was otherwise unremarkable. The arteries were markedly hyalinized. The veins consistently showed an increase in adventitial connective tissue. The malpighian corpuscles were normal.

Stomach: The mucosal lining was thin, the epithelium indistinct. The number of glands was markedly reduced and their basement membranes were prominent. There was a moderate infiltration with lymphocytes. The lamina propria was thickened. The muscularis mucosa and the muscle bundles of the wall were markedly reduced in size.

Small Bowel: The mucosa was thin and the villi were small. Within them the vessels appeared dilated. The muscularis mucosa was thick and fibrous. There was also considerable submucosal fibrosis, in the matrix of which were numerous dilated, congested vascular channels. Both surrounding muscle layers were arranged in loose bundles, widely separated by intervening strands of connective tissue.

Pancreas: The lobules were enclosed by a normal amount of connective tissue. The acinar cells appeared normal, and the ducts were surrounded by a collar of loose, fibrous connective tissue which was undergoing hyalinization. The mucosal cells

of these ducts were swollen and contained reddish granules. The number of islets of Langerhans in each lobule appeared to be increased. The islets were otherwise unremarkable, though their different cell types could not be identified. The arterioles revealed considerable fibrohyaline thickening of their walls.

Kidney: The capsule was of normal thickness. There were many subcapsular scars containing scattered mononuclear cells. In these same areas there were glomeruli which were entirely obliterated by dense masses of hyalinized connective tissue. In other sections the parietal layer of Bowman's capsule showed varying degrees of thickening, and there appeared to be thickening of the glomerular capillary walls. Extension of fibrosis from the glomerular hilus into the tuft was not uncommon. The surrounding tubules revealed abnormal thickening of the basement membranes, which were in continuity with an homogeneous, gelatinous material. In the cortical renal interstitium there was considerable increase in fibrous connective tissue. The arteries and arterioles throughout the sections revealed thickening and hyalinization of their walls.

Urinary Bladder: There was thickening of the submucosal connective tissue. The remainder of the wall was unremarkable.

Prostate: The sections consisted principally of dense masses of fibrous tissue in which there were a few scattered islands of glandular tissue, the epithelium of which varied from columnar to low cuboidal to squamous. Only an occasional gland contained concretions.

Parathyroid: Sections of one parathyroid revealed small scattered circumscribed aggregates of normal water-clear cells surrounded by thin strands of connective tissue. The remainder of the gland consisted of normal cells of the oxyphil type. Sections of another gland revealed a normal capsule and trabeculae with predominant granular oxyphil cells and very few clear cells. There were several small, colloid-filled vesicles.

Thyroid: There was moderate increase in fibrous connective tissue stroma. Follicles varied from some microfollicular structures to those of normal size and organization. There was an occasional area in which small, noncolloid-filled follicles were imbedded in a matrix of fibrous stroma.

Adrenal: The capsule was of variable thickness. In the periadrenal fat there were many small, thick-walled arteries. The cortex was somewhat narrowed and the medullary tissue could not be identified. Three separate cortical layers could not be differentiated, though the method of arrangement of the bulk of the cortex appeared to be zona fasciculata. The cells generally were uniform in size, shape and staining characteristics, though there was some diminution in size as one proceeded from capsule to the center. There were occasional focal aggregates of enlarged, finely granular cells. There was diffuse prominence of the reticulum.

Testicles: The tunica albuginea was markedly thickened and composed of densely packed fibers of elastic and fibrous connective tissue. The seminiferous tubules were normal in size but were uniformly surrounded by a dense tunica propria in which elastic fibers and pink-staining, hyaline-like material was found. The majority of tubules contained cells ranging from spermatogonia through the entire spermatogenic series to spermatozoa. However, the number of cells was reduced, mature spermatozoa were very few, and in many tubules there was no evidence of spermatogenesis. In these, the hyalinized tubular walls were markedly thickened and the lumina narrowed or completely collapsed. In the interstitium there were islands of Leydig's cells with pleomorphic nuclei, and indistinct granular cytoplasm. Many of these cells were surrounded by a hyaline-like material and were undergoing degeneration, so that some islands were almost completely devoid of cells.

Pituitary: The gland was studied by Dr. Sheldon C. Sommers at the Massachusetts Memorial Hospital. Based on a total count of 10,011 cells, no abnormality in the proportions of the cells was found. The differential count was:

Acidophils	3,246	(32.4%)
Basophils	1,947	(19.5%)
Amphophils	2,354	(23.5%)
Chromophobes	2,416	(24.1%)
Hypertrophic amphophils	48	(0.5%)
Hyaline basophils	0	(0%)
Total fields counted	115	

Forearm Skin Biopsy: Thin, atrophic, stratified squamous epithelium covered irregular areas of dense fibrous connective tissue. Deeper in the corium there were a few atrophic hair follicles and sebaceous glands and a few end-arterioles, the walls of which were becoming hyalinized. Around the hair follicles were leukocytic infiltrations.

Brain: Multiple sections from representative areas of the central nervous system were histologically unremarkable.

Discussion

The cardiovascular pathology represents advanced peripheral arteriosclerosis, arteriosclerotic heart disease, myocardial infarction and calcific aortic stenosis. The heart is fundamentally similar to that in the previous autopsy study.[22] The testes and prostate represent the mature expressions of hypoplasia and atrophy, and the kidneys to a lesser extent share in this impression. In Oppenheimer and Kugel's original report the biopsy description of skin was clearly not that of true scleroderma. There is no evidence that diffuse scleroderma occurs in Werner's syndrome, and the cutaneous manifestations of the two diseases have different distributions and characteristics. Familial scleroderma is unknown. These distinctions were emphasized by Thannhauser [4] with detailed histologic support of skin and muscle biopsies, and this impression has since been reaffirmed histologically by Irwin and Ward [23] and with the electron microscope by Reed, Seville and Tattersall.[24] Biopsy in the present case is in accordance with these data. Peripheral arteriosclerosis may modify the natural history of the cutaneous changes in this disorder, but it is not felt to be etiologic. Indeed, the skin disease tends to antedate the vascular lesions, and the ulcers—probably sequelae of pressure rather than vascular insufficiency—are often successfully skin grafted. Though there is no clear understanding of the nature of the skin lesions in Werner's syndrome, the collective impressions suggest hypoplasia and atrophy. The tissues studied by Smith, Winer and Martel [41] had features consistent with pseudoxanthoma elasticum. In view of the specific connotations of the term "scleroderma," it is felt that its use in Werner's syndrome should be abandoned.

Because of the physiologic age of these patients, the relative frequency of neoplasia deserves comment. Up to the present time there are approximately 62 reported cases of Werner's syndrome, of which six had malignant tumors, an incidence of 9.7%. The lesions were melanotic sarcoma,[16] sarcoma of the uterus,[25] fibroliposarcoma,[26] fibrosarcoma and hepatoma,[22] and carcinoma of the female breast.[27] The relative frequency of sarcoma is a point of further interest.

There are nine reports in which appropriate metabolic data are recorded,[3, 16, 22, 23, 24, 25, 27, 32, 25] reflecting physiology of thyroid, parathyroids, gonads, adrenals, pancreas and pituitary. It must be realized that, in a disease with such profound and protracted somatic effects, endocrine function may be variably altered and hence may in turn modify the evolution of the disease. However, critical evaluation of the published data yields no substantial evidence of an etiologically fundamental endocrine disorder in Werner's syndrome. Diabetes, which can vary from mild to severe,[16] and hypogonadism are the only consistently recurring abnormalities of ductless glands. The patient in this study had both of these abnormalities, though the glucose tolerance curves suggested hepatic and starvation effects as well.

A B

FIG. 2. Illustrating the deposits of subcutaneous calcium (A) in the vicinity of the right elbow, and (B) anterior to the left patella.

Only three endocrinopathies are considered to be associated with cataracts:[28] diabetes mellitus, hypothyroidism (cretinism and myxedema), and hypoparathyroidism. Cataracts in Werner's syndrome not only occur far more frequently than the true presenile diabetic cataract, but also may occur before the diabetes is even evident, or indeed, without diabetes at all. Further to illustrate earlier contradictory opinion, both hypoparathyroidism (thin hair, cataracts, dystrophy of nails and abnormalities of skin), and hyperparathyroidism (rarefaction of bone and soft tissue calcification), have been postulated. Abnormal calcium deposition may be grouped as fol-

lows:[29, 30] (1) progressive myositis ossificans, (2) metastatic calcification, (3) calcinosis circumscripta and calcinosis universalis, (4) dystrophic calcification (in dead, devitalized or degenerated tissue), (5) arterial calcification, and (6) lithiasis (renal, biliary, salivary). In Werner's syndrome there is advanced arteriosclerotic calcification, well illustrated by the present case, which also had calcium deposited in an old myocardial infarction. Of further interest is the localization of calcium in skin and subcutaneous tissues of the extremities, which should properly be called calcinosis circumscripta (figure 2). The large, widespread deposits involving skin as well as deeper structures of the entire body (calcinosis universalis) has not been described in this syndrome, though it is of interest that one case of calcinosis universalis with premature senility has been reported.[31] In the autopsy case of Oppenheimer and Kugel [22] there were some deposits of calcium in the lumina of renal tubules, and the histologic changes in the parathyroids (of which only two were found) were believed to indicate increased activity. Though mild hypercalciuria was present, additional metabolic corroboration was unconvincing, and the subsequent studies referred to above, especially those of Erwin, would indicate that there is no basic physiologic abnormality of parathyroid glands in Werner's syndrome. The aggregates of clear cells in a single parathyroid in the present autopsy had no apparent physiologic counterpart. Detailed study of the anterior hypophysis revealed a normal cell distribution. The alterations in the adrenal glands, especially the cell aggregates, must be noted, but similar findings are common in autopsy material and have no apparent physiologic significance. However, Bauer and Conn [32] felt that Werner's syndrome might be an unusual form of adrenocortical hyperfunction, manifesting itself by such features as failure to grow and develop normally, frequent diabetes, osteoporosis, and evidence of tissue atrophy suggesting antianabolic effects of prolonged duration. In their single case, the adrenocortical and metabolic responses to ACTH were normal, but because of decreased excretion of 17-ketosteroids and increased excretion of formaldohydrogenic steroids in recovery and control periods, it was felt that there might be a selective hepatic inability to convert endogenous 17-hydroxycorticoids into excretory 17-ketosteroids. Although the patient had no laboratory evidence of liver disease (moderate hepatomegaly was present, however), the data suggested that the liver was unable to convert orally administered Compound S (11-desoxy 17-hydroxycorticosterone) into excretory 17-ketosteroids. Since metabolically active hydrocortisone is felt by these investigators to be similarly converted by the liver, it was postulated that in Werner's syndrome there may perhaps be a state of chronic hyperhydrocortisonism. This need not be invalidated by the pronounced excretion of 17-ketosteroids when the patient's adrenals are stimulated by ACTH, since there is evidence [33] that the hepatic enzyme system responsible for the conversion of hydrocortisone can be selectively impaired, allowing normal conversion and excretion of other corticosteroids. It is necessary,

however, to point out that even if such a metabolic defect does exist in Werner's syndrome, one need not conclude that its sequel is an elevation of plasma hydrocortisone. In the presence of diminished hepatic degradation of Compound F, its endogenous production may decrease, resulting in a normal plasma level.[33] It might also reasonably be observed that if the relatively small amount of Compound F excreted as 17-ketosteroids diminishes, its excretion as formaldohydrogenic (11 oxy) steroids might increase. The consequence of this physiologic adjustment could, indeed, be a low urinary 17-ketosteroid excretion, with the excess Compound F eliminated as formaldohydrogenic steroids, thus maintaining a normal plasma level of hydrocortisone.

Though it is felt that many of the gross and histologic changes described in this study could in part be reflections of senility and protracted cachexia,[34] the prominence of the alterations of connective tissue deserves additional though cautious comment. This prominence is not confined to the necropsy material, but is, indeed, consistent with many features of the clinical picture and natural history of the disease. The "abiotrophic" abnormalities of connective tissue may thus be of fundamental significance, and the familial background of the disorder further suggests that these abnormalities may be genetically determined.

Summary

The clinical and postmortem material in a case of Werner's syndrome are presented, with a review of this syndrome and of allied disorders. Attention is called to the relative frequency of neoplasia, especially sarcoma, an association not hitherto emphasized. Although our observations have permitted some conclusions of interest, neither this autopsy nor that of Oppenheimer and Kugel has solved the etiologic problem. The evidence, however, would appear effectively to exclude the endocrine glands as etiologically fundamental. One is left with the impression that Werner's syndrome is a hereditary "abiotrophic" disorder which, in some as yet unknown fashion, reflects itself either as the isolated "forme fruste" or as the profound somatic disturbance of the complete disease state.

Acknowledgment

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Summario in Interlingua

Es presentate un revista del syndrome de Werner, insimul con constatationes clinic e post morte in un caso que es le secunde venite al necropsia. Le morbo es heredofamilial. Illo occurre equalmente in masculos e femininas. Usualmente illo

se manifesta primo durante le decennio post le adolescentia. Le spectro del aspectos clinic include obstruction del crescentia, capillos gris e calvitia, perdita de histos subcutanee e del massa muscular in le extremitates, atrophic alterationes hyperceratotic in le pelle acral e facial con callositates, arthrogryposis, ulceres indolente, e calcification subcutanee, cataractas que progrede gradualmente, frappantemente prematur arteriosclerosis e morbo del arteria coronari, subdisveloppamento sexual, diabete, osteoporosis, e arthritis hypertrophic.

Es presentate un re-evalutation del relation inter le syndrome de Werner e le sequente distincte sed apparentemente affin entitates pathologic: Syndrome de Rothmund, cataracta dermatogene, dysplasia ectodermal hereditari, dystrophia myotonic, e progeria con nanismo. Le separation del syndrome de Werner ab scleroderma es reconfirmate.

Le presente studio, que comprendeva un revista critic del publicate datos metabolic e un detaliate investigation histologic del glandulas sin canal excretori (incluse le numeration cellular pituitari), justificava le sequente conclusiones: Ni le necropsia del presente caso ni le necropsia publicate per Oppenheimer e Kugel ha producite datos convincente de major signification etiologic. Investigationes metabolic corrobora le constatationes necroptic e pare de facto excluder le glandulas endocrin como etiologicamente de importantia fundamental. On ha le impression que le syndrome de Werner es un disordine "abiotrophic" de determination genetic, le qual —in un maniera ancora completemente incognoscite—se reflecte como le *forme fruste* in isolation o como le profunde disturbation somatic del complete stato pathologic. Es etiam signalate le frequentia relative de neoplasia—specialmente sarcoma—in syndrome de Werner. Iste association ha non previemente essite relevate.

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ANURIA DUE TO CARBON TETRACHLORIDE INTOXICATION *

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INTRODUCTION

THERE are many drugs and chemicals which can produce renal injury resulting in acute urinary suppression. Among these is carbon tetrachloride,[1, 2] which is widely used as an industrial solvent, as a household cleanser, as a vermifuge, and as a constituent of some types of fire extinguishers. This report is a clinical analysis of 20 patients with anuria due to carbon tetrachloride intoxication seen at the Peter Bent Brigham Hospital between 1948 and 1957.

RESULTS

Of the 20 cases, 16 were male and four were female. Their ages varied from 23 to 49 years. There were five deaths, or a mortality of 25%. Ten of these patients underwent hemodialysis with the Kolff-Brigham artificial kidney. Three of these subsequently died.

Exposure by Inhalation or Ingestion: Sixteen of the patients suffered intoxication by inhalation and four by ingestion of carbon tetrachloride. Eleven cases by inhalation resulted from the use of carbon tetrachloride as a cleaning agent. Either cleaning furniture at home or machinery at work was the characteristic story. Usually the room in which the cleaning occurred was poorly ventilated or completely closed. Exposure time ranged from 30 minutes to 11 hours. Two patients inhaled fumes from fire extinguishers which contained carbon tetrachloride. One patient inhaled the fumes from a broken jug of carbon tetrachloride for 30 minutes while cleaning it up in the basement. Another had sprayed the interior of his house with carbon tetrachloride in an effort to delouse it. A third was filling aerosol bombs with carbon tetrachloride for a period of approximately eight hours. Three of the 16 patients inhaling carbon tetrachloride died.

Of the four whose poisoning occurred by ingestion, two died. One patient attempted suicide by drinking 15 c.c. Two others drank small amounts supposedly by mistake; both had been drinking alcohol at the time.

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The fourth patient consumed 4 oz. of carbon tetrachloride which was stored in a tonic bottle.

Alcoholic History: Sixteen of the 20 patients had consumed large quantities of alcohol daily for a period of months or years. Fourteen of these 16 admitted taking alcohol either shortly before, during or shortly after exposure to carbon tetrachloride. Two patients were not heavy drinkers but had ingested alcohol at the time of exposure to carbon tetrachloride. There were several instances where fellow workers were exposed at the same time but suffered no apparent ill effects. In at least one of these cases the fellow worker had consumed no alcohol.

Previous Renal Disease: Eighteen of the nineteen gave no history of previous renal disease. One patient had had a ureteral stone removed 15 months prior to exposure to carbon tetrachloride.

Liver Involvement: All four patients with intoxication via the oral route suffered severe liver involvement. This was proved in one by postmortem examination. The other three had definite clinical and laboratory evidence of hepatic dysfunction. Two of these three experienced hepatic coma.

Five patients of the 16 suffering intoxication by inhalation had no demonstrable liver involvement. The remaining 11 had moderate to severe damage.

Bleeding Diathesis: Twelve of the 20 patients had evidence of hemorrhage, manifested as subconjunctival hemorrhages, petechiae or bleeding from the nose. Furthermore, two of these 12 had severe gross bleeding from the genitourinary tract. This was accompanied by renal colic in one patient.

Clinical Features: The earliest and most common symptoms were nausea and vomiting, which manifested themselves from one hour to six days after exposure. Usually, however, the patient felt ill within a matter of hours. Abdominal pain and costovertebral pain were not uncommon. One patient was operated on for what was thought to be acute appendicitis. Other symptoms were headache, confusion and fatigue.

The number of days between exposure to carbon tetrachloride and the development of anuria was often difficult to determine accurately. In those in whom it was possible, it varied from one to seven days, with an average of three. Anuria persisted from one to 15 days, with an average of eight. The degree of azotemia at its peak ranged from a blood urea nitrogen of 97 to one of 305 mg.%. Three patients experienced pulmonary edema, but this was due to overhydration. Urine examinations were typical of those commonly encountered in acute tubular necrosis, with proteinuria, red and white blood cells, and hyaline, granular and red cell casts.

The clinical features are illustrated in the following two typical histories.

Case Reports

Case 1. A 42 year old American seaman was admitted to another hospital on January 2, 1955, because of five days of vomiting. On December 28, 1954, he had

cleaned a marine engine with a half-pail of carbon tetrachloride in a closed compartment. He was exposed for approximately two hours, and vomiting started several hours later. He denied any recent ingestion of ethanol. He complained of abdominal pain. His past history was essentially negative except for a large alcoholic intake when he was in port. Physical examination revealed epigastric and bilateral costovertebral angle tenderness. The liver was enlarged two fingerbreadths below the right costal margin, but was not tender. X-ray of the chest revealed the lung fields to be clear and the heart to be of normal size. Urinalysis revealed 4 plus proteinuria, 25 to 30 red blood cells per high power field, and many white blood cells with clumping. Blood urea nitrogen was 218 mg.%; total bilirubin, 2 mg.%; serum sodium, 120 mEq./L.; potassium, 7.2 mEq./L.; chloride, 74 mEq./L.; CO_2, 13 mEq./L. An electrocardiogram showed evidences of potassium intoxication. The urine output was below 500 c.c. per day. When on January 6, 1955, during an infusion of 10% glucose and water, the patient developed pulmonary edema, he was transferred to the Peter Bent Brigham Hospital for possible hemodialysis.

On admission the signs and symptoms of pulmonary edema were present. Five hundred cubic centimeters of blood were removed, with decrease in the patient's respiratory difficulties. During the physical examination his reflexes became unobtainable and his electrocardiogram showed changes of severe potassium intoxication. Two hundred cubic centimeters of 3% sodium chloride were administered intravenously; 2 gm. of calcium gluconate were also added. Five hundred cubic centimeters of 20% dextrose and water, plus 100 units of regular insulin, were started. The electrocardiogram showed dramatic changes toward normal, and reflexes returned to normal. While the patient was being prepared for hemodialysis an electrocardiogram again showed advanced changes of hyperkalemia. Sodium chloride and calcium gluconate were again administered intravenously. Dialysis was begun immediately following this infusion. The electrocardiogram during dialysis showed decreasing potassium effect. Blood chemistries before dialysis were: serum potassium, 8.2 mEq./L.; CO_2, 13.8 mEq./L.; blood urea nitrogen, 206 mg.%; serum sodium, 118 mEq./L.; serum chloride, 72 mEq./L. Blood chemistries following dialysis were: serum potassium, 4.7 mEq./L.; CO_2, 19.2 mEq./L.; blood urea nitrogen, 155 mg.%; serum sodium, 126 mEq./L.; serum chloride, 90 mEq./L. Dialysis was performed for four hours.

Urine output steadily increased until by the eleventh hospital day the patient's output was 3,400 c.c. Except for hiccups, which finally disappeared, he had an uneventful recovery.

Case 2. A 39 year old white male was transferred to the Peter Bent Brigham Hospital on December 19, 1952, because of anuria. On December 7, 1952, 12 days prior to admission, he had ingested 4 oz. of carbon tetrachloride. He had asked one of the children in the family to bring him a bottle of tonic. The child had brought a "7 Up" bottle from the back porch which, unfortunately, had carbon tetrachloride in it. Immediately following ingestion of this he was given 1.5 oz. of rye whiskey. One hour later the patient took mustard and began to vomit. He ingested large quantities of liquids that night and continued to vomit. The next day, December 8, he attempted to work but was unable to. He vomited profusely on December 8 and 9. On December 12 be became disoriented and was admitted to another hospital. There the history was obtained that his urine output had decreased and had also become dark. He had also noticed his sclerae were yellow. Nonprotein nitrogen was 108 mg.%, and serum bilirubin was 7 mg.%. Serum potassium was 6 mEq./L. He was restricted to 400 c.c. of fluid by mouth per day and given approximately 1,000 c.c. of 10% dextrose and water by vein. His urine output varied from 50 c.c. to 160 c.c. per day. His clinical situation steadily worsened. On December 18, because of a rising serum potassium and electrocardiographic evidence of potassium intoxication, an ex-

change transfusion was performed, and was he given a gastric lavage of 5,000 c.c. of distilled water, of which all but 500 c.c. was recovered.

In March, 1952, he had had a ureteral calculus removed. There was no previous history of hypertension.

Physical examination on admission to the Peter Bent Brigham Hospital revealed an acutely ill man who was comatose. The eyes rolled upward and did not react to light. Skin was icteric. There was generalized twitching. The mouth was filled with old clotted blood, and the tongue was bitten. There was some dullness in the right lower lung, but no râles were heard. The heart was not enlarged, and no murmurs were heard. Blood pressure was 160/70 mm. of Hg; pulse, 80. The liver was palpable three fingerbreadths below the right costal margin. The rectum was prolapsed and the mucosa was necrotic. Laboratory examination revealed a hematocrit of 46%, a leukocyte count of 14,200. Examination of the urine showed: specific gravity, 1.010; pH, 6; protein, 3 plus; sugar, trace; bilirubin, 3 plus. Urinary sediment revealed 0 to 3 red blood cells per high power field and 2 to 6 white blood cells per high power field, with rare granular casts. Blood chemistries were: blood urea nitrogen, 184 mg.%; CO_2, 20 mEq./L.; serum chloride, 74 mEq./L.; serum sodium, 110 mEq./L.; serum potassium, 6.1 mEq./L.; fasting blood sugar, 62 mg.%; serum calcium, 3.9 mEq./L.; serum phosphorus, 3 mEq./L. Bilirubin was 10.65 mg.%. An electrocardiogram was consistent with potassium intoxication. The first night in this hospital the patient was given 400 c.c. of 3% saline because of potassium intoxication. On the second hospital day hemodialysis was performed with the Kolff-Brigham artificial kidney. Chemistries following dialysis were: blood urea nitrogen, 39 mg.%; chloride, 100 mEq./L.; sodium, 128 mEq./L.; potassium, 3.4 mEq./L. The patient had several convulsions toward the end of dialysis. There seemed to be no clinical improvement. Convulsions continued the next day and could not be controlled with drugs. Urine output remained below 300 c.c. per day. On the fourth hospital day he died. Permission for autopsy was denied.

Hemodialysis: Dialysis was performed in 10 patients. The number of days the patient had been anuric before dialysis was instituted varied from four to 14, the average being eight. All patients had a good biochemical response, and approximately 80% had a favorable clinical response to dialysis. The indications for dialysis varied. Two patients showed electrocardiographic evidence of severe potassium intoxication. The remainder of the patients had various central nervous system manifestations of the uremic syndrome. Some of the these could have been due to coexistent hepatic insufficiency. Five patients were in frank coma, while several others were severely somnolent, with Cheyne-Stokes respirations. It was interesting to note that several patients (but not all) who were suffering from hepatic insufficiency (flapping tremor) had a good clinical response to dialysis. Three subsequently died.

Cause of Death: There were five deaths, and autopsies were performed on four. The cause of death, as determined clinically, in the patient on whom no postmortem examination was done, was severe hepatic insufficiency. Two others died of hepatic insufficiency, and this was substantiated by the findings at postmortem examination. In one of these a further complication of severe bleeding in the posterior pharynx occurred. This appeared when the patient was heparinized before undergoing her second di-

alysis. One patient died of severe bronchopneumonia. Another died of pulmonary edema due to overhydration. It should be emphasized that all these patients had many abnormalities, the exact cause of death often being difficult to determine. Postmortem examination revealed acute tubular necrosis of the kidneys and severe central necrosis of the liver in all four patients. Ancillary abnormalities were pancreatitis and pulmonary edema.

Discussion

It is well known that the ingestion of alcohol at or near the time of exposure to carbon tetrachloride greatly predisposes the patient to the serious effects of the chemical. This was certainly borne out in this series. Carbon tetrachloride is soluble in alcohol,[3] and the ingestion of alcohol and carbon tetrachloride simultaneously may tend to increase the absorption of the latter. If exposure was by inhalation, and if alcohol was also being excreted at the same time via the lungs, or was present in the blood in significant concentration, it seems possible that the absorption of carbon tetrachloride might also be enhanced.

However, because the ingestion of alcohol *after* exposure to carbon tetrachloride also appears to predispose to serious injury, it may be that it is not an enhancement of absorption of carbon tetrachloride by alcohol which is responsible for this predilection. It is known that carbon tetrachloride can be oxidized to phosgene, and that phosgene in vitro can condense with ethanol to form ethylchloroformate.[4] One can speculate that possibly this sequence of events can occur in vivo. In the absence of ethanol, phosgene can condense in vitro with ammonia to form urea, a harmless substance. It would indeed be interesting to determine the toxicity of ethylchloroformate, and to look for its presence in experimental animals exposed to both carbon tetrachloride and ethanol.

Whether the chronic drinker who has not recently ingested alcohol is more susceptible to carbon tetrachloride intoxication is not clearly understood. If a fatty liver is present (carbon tetrachloride being soluble in fat), or definite hepatic insufficiency, the liver would probably be more susceptible to damage. Recent work in animals has indicated that the kidney may show a definite lesion due to choline deficiency [5, 6] which can be enhanced by alcohol.[7] Possibly the kidney of the chronic alcoholic patient is more susceptible to injury.

There are multiple explanations for the bleeding tendency seen in this series. All patients were azotemic, and many had severe hepatic damage with a greatly prolonged prothrombin time. Some animal work has indicated that carbon tetrachloride is directly injurious to the capillaries.[8] As mentioned previously, two patients experienced severe gross hematuria. In one of these, however, bleeding and coagulation times, platelet count and prothrombin time were all within normal limits.

It has been stated that when carbon tetrachloride is ingested, liver dam-

age predominates. When intoxication occurs by inhalation, the kidney is much more likely to be damaged also.[1] Since only patients with significant renal damage were included in this series, it is difficult to comment on the above. However, all patients in this series who ingested carbon tetrachloride suffered severe hepatic damage.

The exact cause of death was often difficult to determine, but clinically and according to postmortem findings it was thought in most cases to be hepatic insufficiency.

Acute tubular necrosis resulting from carbon tetrachloride intoxication is clinically and morphologically indistinguishable from that due to other insults. Thus the treatment of patients included in this series was the same as that administered to patients with tubular necrosis from any cause. This has been outlined in detail elsewhere.[9] The only effective means of preventing anuria due to carbon tetrachloride is the education of the public and industry concerning the hazards of its use.

Summary

Twenty cases of acute carbon tetrachloride intoxication resulting in anuria are reported. This was caused by inhalation in 16 cases and by ingestion in four.

Summario in Interlingua

Es discutite 20 casos de intoxication per tetrachloruro de carbon con consequente anuria. Dece-sex del patientes esseva mascule, quatro feminin. Le intoxication habeva resultate de inhalation in 16 casos e de ingestion in quatro. Omne le patientes, con le exception de duo, presentava un historia de consumption de alcohol. Le ingestion de alcohol a o circa le tempore del exposition a tetrachloruro de carbon augmenta grandemente le probabilitate de intoxication. Mechanismos possibile de iste relation es discutite. Le prime symptomas (e le plus commun) esseva nausea e vomito occurrente inter un hora e sex dies post le exposition. Usualmente iste symptomas esseva manifeste intra alicun horas. Anuria superveniva inter un e septe dies post le exposition. Le duration medie de iste intervallo esseva tres dies. Cinque patientes moriva. In tres le causa esseva insufficientia hepatic; in un, bronchopneumonia; e in un, edema pulmonar. Acute necrosis tubular esseva morphologicamente demonstrabile in omne le necropsias. Il seque que le tractamento de anuria causate per intoxication per tetrachloruro de carbon es identic con le tractamento usate in patientes con acute necrosis tubular ab non importa qual causa. Hemodialyse esseva effectuate in 10 patientes. Le responsa biochimic al dialyse esseva bon in omne casos. In circa 80% del casos etiam le responsa clinic esseva favorabile.

Le sol efficace medio pro le prevention de intoxication per tetrachloruro de carbon es educar le publico e le gerentes industrial con respecto al hasardos de su uso.

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A NEW CONCEPT IN THE TREATMENT OF PENICILLIN REACTIONS: USE OF PENICILLINASE * †

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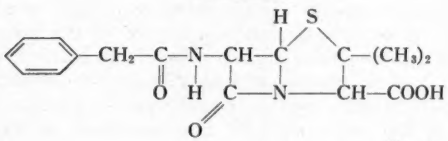
A PREVIOUS report [1] described the in vivo action of penicillinase on circulating penicillin in guinea pigs and human subjects without reactions. The following is a report of the clinical effectiveness of penicillinase in humans with penicillin reactions.

Penicillinase [2] is an enzyme specific for its substrate penicillin. Its inactivating action against penicillin has been utilized for years in the clinical laboratory in bacteriologic media to inhibit penicillin in body fluids to be cultured. Penicillinase can be obtained from several strains of bacteria, including staphylococci and *Escherichia coli.* Commercially it is produced in greatest abundance from cultures of *Bacillus cereus,* strain NRRL-B 569 (Schenley Laboratories). The precipitation and purification of the enzyme are described in the initial report.[1]

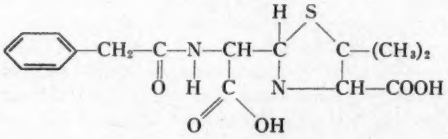
The inactivating action of penicillinase is through its catalytic hydrolysis of the lactam ring of the penicillin molecule, changing penicillin to penicilloic acid,[2, 3] which is nonantigenic in this sensitivity system.[1]

Penicillin G



P-ase

Penicilloic Acid



In the original study it was found that in guinea pigs and humans without reactions who had received penicillin, and in whom consistent penicillin blood levels were established, no circulating penicillin could be found within

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† The penicillinase used in these studies was generously supplied by Schenley Laboratories, Inc., New York, N. Y., through the courtesy of Dr. B. Marr Lanman, Director of Clinical Research, and Dr. Bruno Puetzer, Director of Research.

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an hour or less after a parenteral injection of penicillinase. No toxic effects from penicillinase were noted clinically or histologically.

In this study, patients with penicillin reactions were given penicillinase intramuscularly, in single or multiple injections, and the results recorded.

Case Reports

Case 1. A 39 year old white male was given 2,000,000 units of benzathine penicillin (Bicillin) intramuscularly.

Reaction: There was minimal swelling of the hands and knuckles within two days, which receded in one day. Ten days following the administration of Bicillin, however, the patient developed extensive giant urticaria and extensive angio-edema, with joint involvement of the serum-sickness type.

Treatment: Cortef, 20 mg. four times a day; Benadryl, 50 mg. four times a day; and adrenalin in oil daily. Since after two days the reaction continued to increase in severity, 1,000,000 units of penicillinase were given intramuscularly.

Result: Complete clearing of the urticaria was noted within 24 hours, and the angio-edema and joint involvement cleared within 48 hours after administration of penicillinase.

Toxicity: None.

(Courtesy Dr. John Davis, Markesan, Wisconsin.)

Case 2. A 47 year old white male received 300,000 units of fortified procaine penicillin daily for two days intramuscularly.

Reaction: Ten days after receiving penicillin he developed tiny vesicles on the hands, which were followed by weeping and cracking of the skin; three days later there was severe generalized urticaria, associated with difficulty in breathing and swallowing.

Treatment: The patient was given 1,000,000 units of penicillinase 24 hours after the appearance of urticaria and four days after exudative dermatitis of the hands; he also received 50 mg. of Pyribenzamine orally at the time of the penicillinase injection.

Result: Within three hours the patient developed chills, his breathing improved, and within 24 hours all of the giant urticaria and dermatitis had disappeared except for a small area on the medial aspect of the left upper arm.

Toxicity: The local pain at the site of the injection in the arm persisted for 36 hours, and the transitory chills for three hours after the injection; otherwise, no side effects were noted.

(Courtesy Dr. Everett H. Johnson, Turlock, California.)

Case 3. A 40 year old white female received 1,200,000 units of fortified procaine penicillin for five injections over a period of two weeks intramuscularly.

Reaction: Nine days later generalized giant urticaria developed, with angio-edema of the hands, feet and face.

Treatment: Only penicillinase, 1,000,000 units intramuscularly, given 14 hours after the reaction started.

Result: Complete clearing of urticaria and angio-edema in 20 hours.

Toxicity: None.

Case 4. A 25 year old white male received 800,000 units of fortified procaine penicillin intramuscularly once on August 1, twice on August 2, and once on August 3.

Reaction: A generalized giant urticaria developed on August 9, with marked angio-edema of face, hands and feet.

Treatment: Oral Pyribenzamine, 50 mg. four times a day, prednisolone, 5 mg. four times a day from August 9 to August 11, with no effect on either the urticaria or the angio-edema. Penicillinase, 1,000,000 units intramuscularly, was given on August 10 and again on August 13.

Result: Complete clearing 36 hours following the August 13 penicillinase injection.

Toxicity: None.

Case 5. A 52 year old white male was given 600,000 units of procaine penicillin intramuscularly.

Reaction: One to two hours after the injection a rash appeared. After onset the generalized urticaria became chiefly an exfoliative papular dermatitis of the face, feet and hands, but later involved the entire body.

Treatment: Initially Sandostene with calcium was used, with no benefit. Steroids were avoided because of the presence of diabetes and an ulcer. Penicillinase, 1,000,000 units intramuscularly, was given approximately seven days after the reaction started.

Result: "Dramatic clearing of patient's extensive and markedly pruritic dermatitis within 18 hours in a situation where steroids had to be avoided."

Toxicity: None.

(Courtesy Dr. Ely Perlman, New York, N. Y.)

Case 6. A 52 year old white male received benzathine penicillin (Bicillin), intramuscularly, 1,000,000 units daily on May 28, 29, 30 and 31, 1956.

Reaction: Generalized urticaria, angio-edema and joint swelling with redness and inflammation.

Treatment: Benadryl, Teldrin, Pyribenzamine; prednisolone, 2.5 mg. four times a day for one week, 5 mg. four times a day for one week, 5 mg. twice a day for two days, 5 mg. five times daily for three days; it was then stopped for four days; then 5 mg. four times a day for four days, and stopped for 10 days, then 5 mg. four times a day for one week, all without apparent relief. Penicillinase was started, 1,000,000 units intramuscularly, on July 25, 1956, and repeated on July 28, August 4 and August 7, 1956.

Result: Complete clearing of hives, edema and joint inflammation following 1,000,000 units of penicillinase on August 7, 1956.

Toxicity: None.

(Courtesy Dr. F. M. Hummer, Madison, Wisconsin.)

Case 7. A 36 year old white male was given "penicillin tablets."

Reaction: Generalized urticaria and severe angio-edema which came on about 10 days to two weeks following ingestion of the penicillin.

Treatment: Patient received only penicillinase, 3,000,000 units intramuscularly.

Result: Clearing of lesions within 48 hours. The urticaria and angio-edema recurred in about one week, and there was complete clearing after another 3,000,000 units penicillinase intramuscularly. (The clinician felt that in this case the penicillinase was of great benefit.)

Toxicity: None.

(Courtesy Dr. Jerome Glaser, Rochester, N. Y.)

Case 8. A 35 year old white male was given 800,000 units of fortified procaine penicillin daily for three days intramuscularly.

Reaction: Serum-sickness type, with generalized urticaria, angio-edema and swollen, inflamed joints.

Treatment: Only penicillinase was used, 640,000 units intramuscularly, 12 hours after the reaction started.

Result: Partial clearing of edema in 24 hours, complete clearing of urticaria in 24 hours, complete clearing of edema and joint involvement in 48 hours.

Toxicity: None.

Case 9. A 28 year old white female was given 1,200,000 units of fortified procaine penicillin every third day for three doses, intramuscularly.

Reaction: Generalized giant urticaria, with early serum-sickness type of arthritis of the hands and feet.

Treatment: Only penicillinase was used, 1,000,0000 units 24 hours after reaction started.

Result: Complete clearing of all urticaria and edema in 30 hours.

Toxicity: None.

Case 10. A 47 year old white male received procaine penicillin, 1,200,000 units total in one week intramuscularly.

Reaction: Erythema, edema and severe pruritus of the hands and feet.

Treatment: Only penicillinase was used, 1,000,000 units intramuscularly 24 hours after onset of reaction.

Result: Complete clearing of symptoms and complaints 72 hours after penicillinase.

Toxicity: None.

(Courtesy Dr. R. H. Snapp, Phoenix, Arizona.)

Case 11. A 59 year old white female received benzathine penicillin (Bicillin) tablets orally, 200,000 units nine doses.

Reaction: Generalized urticaria over the entire body, with diffuse urticarial dermatitis in the antecubital, popliteal and crural areas.

Treatment: Two million units of penicillinase were started three days after the reaction, Chlor-trimeton on the third day after penicillinase, and prednisolone on the fifth day after penicillinase.

Result: Nearly all hives disappeared within 24 hours, all within 48 hours. The dermatitis in the skin folds was improved but persisted to some extent, so Chlor-trimeton and prednisolone were used.

Toxicity: None.

(Courtesy Dr. John A. Beyer, Madison, Wisconsin.)

Case 12. A 55 year old white male was given 1,200,000 units of procaine penicillin intramuscularly three times in one week.

Reaction: About 10 days later, severe generalized urticaria, with angio-edema of hands, feet, lips and eyes.

Treatment: Only penicillinase, 640,000 units intramuscularly, 24 hours after reaction started.

Result: Urticaria gone in 24 hours, swelling of hands and lips and eyes in 48 hours.

Toxicity: None.

Case 13. A 41 year old white male was given 600,000 units of procaine penicillin intramuscularly every other day for three days.

Reaction: Generalized urticaria, slight angio-edema.

Treatment: One million units of penicillinase intramuscularly, given within 24 hours after reaction.

Result: Completely cleared within 36 hours.

Toxicity: None.

Case 14. A 16 year old white female was given 1,000,000 units of benzathine penicillin (Bicillin) intramuscularly two weeks before reaction.

Reaction: Generalized urticaria, angio-edema of the face, hands and feet, serum-sickness type, with red, swollen joints in hands and ankles.

Treatment: Had received two tablets of an antihistamine without effect. Two million units of penicillinase were given intramuscularly four days after the reaction and repeated four days later.

Result: Urticaria and edema cleared in 48 hours, the inflamed joints in about 72 hours.

Toxicity: None.

Case 15. A 23 year old white female received 300,000 units of benzathine penicillin (Bicillin) and 300,000 units of procaine penicillin intramuscularly daily for two days.

Reaction: Giant urticaria of arms, forearms, legs, thighs and buttocks. Diffuse swelling of face, hands and feet; intense pruritus beginning 10 days after penicillin, severe on the eleventh day.

Treatment: Only penicillinase, 2,000,000 units intramuscularly, given on the day the severe reaction was noted.

Result: A 90% clearing of lesions and symptoms in 24 hours. Complete clearing in 48 hours.

Toxicity: None.

(Courtesy Dr. C. Doehlert, Madison, Wisconsin.)

Case 16. A 53 year old white female received 600,000 units of penicillin and streptomycin intramuscularly for two doses.

Reaction: Severe giant urticaria with plaques 3 to 5 cm. in diameter covering neck, arms, legs and abdomen.

Treatment: Penicillinase, 1,000,000 units three weeks after penicillin, and repeated five weeks after penicillin. (Time after reaction started not noted.) Patient also given Phenergan, 12.5 mg. four times a day for two weeks, ACTH, 80 units twice.

Result: Marked improvement six days after the injection of penicillinase. Patient was seen two and one-half months after penicillinase, with no recurrence. "Although this patient received adjuvant therapy consisting of an antihistamine and ACTH, her response to therapy appeared to be better than that obtained with patients previously treated without penicillinase."

Toxicity: None.

(Courtesy Dr. Charles R. Rein, New York, N. Y.)

Case 17. A female received 600,000 units of procaine penicillin intramuscularly twice daily for seven days.

Reaction: On the eighth day she developed severe giant urticaria on the trunk, and moderately severe giant urticaria on the extremities.

Treatment: One million units of penicillinase intramuscularly, prednisolone, 15 mg. every six hours, Benadryl, 25 mg. every six hours, calamine lotion with phenol every four hours.

Result: "She made a very rapid response with complete clearing of urticaria within 12 hours. The above response was rather dramatic, and I tend to feel that penicillinase was a very desirable measure with this patient."

Toxicity: None.

(Courtesy Dr. R. M. Bell, Charlotte, North Carolina.)

Case 18. A 54 year old white male received penicillin, "several injections," intramuscularly.

Reaction: One month after the injections, generalized pruritic urticarial erythematous lesions appeared.

Treatment: Penicillinase, 1,000,000 units given three months after onset of reaction. Previous therapy had consisted of ACTH, cortisone and Benadryl. After the penicillinase the only other therapy was a lotion and chloral hydrate.

Result: Slow clearing of lesions over a period of eight weeks following penicillinase, with complete clearing at the end of this time.

Toxicity: None.

Case 19. A 60 year old white female received 600,000 units of procaine penicillin in one intramuscular injection.

Reaction: Generalized severe urticaria two weeks later.

Treatment: Meticorten, 5 mg. four times a day for three days, with no apparent effect. Then 1,000,000 units of penicillinase, given intramuscularly and repeated in three days.

Result: Considerable subjective and objective improvement (75%) in 24 hours after the first injection of penicillinase, practically complete response to second injection of penicillinase. "Apparently excellent response."

Toxicity: None.

(Courtesy Dr. J. S. Bagwell, Dallas, Texas.)

Case 20. A 37 year old white male received procaine penicillin, 600,000 units intramuscularly every other day for three doses.

Reaction: Delayed urticaria and serum-sickness type, appearing two weeks after last dose of penicillin.

Treatment: Various antihistamines were used, with little amelioration of symptoms. Seven weeks after onset of reaction 1,000,000 units of penicillinase were given intramuscularly, and 1,000,000 units again four days later.

Result: Signs and symptoms somewhat lessened in intensity, but no striking improvement.

Toxicity: None.

(Courtesy Dr. Ely Perlman, New York, N. Y.)

Case 21. A 71 year old white male received 3,600,000 units of procaine penicillin intramuscularly.

Reaction: Urticaria, joint swelling and tenderness, angio-edema of the feet and scalp, purpuric type of skin lesions.

Treatment: One dose ACTH and many antihistamines, without much apparent relief. Two weeks after onset of reaction, 1,000,000 units of penicillinase were injected intramuscularly.

Result: Decrease in severity of symptoms following penicillinase.

Toxicity: Marked local swelling 10" across area of right buttock.

(Courtesy Dr. Ely Perlman, New York, N. Y.)

Case 22. A 53 year old white female received "several injections" of procaine penicillin intramuscularly.

Reaction: Weeping, exudative dermatitis involving the face, neck and hands, with marked periorbital edema.

Treatment: No response to local dermatologic dressings for four weeks. Then the patient was given 2,000,000 units of penicillinase intramuscularly, repeated in 48 hours.

Result: Dramatic and complete clearing of lesions within 48 hours of the second injection of penicillinase.

Toxicity: None.

(Courtesy Dr. Eugene Juster, Madison, Wisconsin.)

Case 23. A 32 year old white male was given two injections of benzathine penicillin (Bicillin) intramuscularly.

Reaction: Inflamed, swollen left ankle, severe generalized giant urticaria with extreme pruritus, tenderness in joints coming on two weeks after the initial Bicillin injection.

Treatment: Epinephrine HCl, 0.25 c.c. subcutaneously, repeated at different intervals; Benadryl, 50 mg. four times a day; Meticorten, 5 mg. three times a day, with no relief over the next three days. Five days later, 1,300,000 units of penicillinase were given intramuscularly. On the following day Meticorten, 5 mg. twice a day, and penicillinase, 200,000 units intramuscularly.

Result: The patient symptomatically improved rapidly. His joint swelling and urticaria completely subsided in the next 24 hours. He remained asymptomatic for one week, then developed urticaria again. This was milder and was treated with Benadryl and Meticorten alone, with a good result.

Toxicity: None.

(Courtesy Dr. R. B. Gooder, Flint, Michigan.)

Case 24. A 35 year old white female was given 2 c.c. benzathine penicillin (Bicillin) intramuscularly on January 12, 1957.

Reaction: Onset of generalized urticaria, periorbital and lip swelling on the morning of January 21. Palmar edema and marked swelling of left wrist and ankle. Paresis of right leg and foot; "injection of Bicillin had been in right buttock."

Treatment: Two million units of penicillinase were given at 8:30 p.m. on January 21; ACTH gel, 40 units on January 31, February 2 and February 4; Sterane, 5 mg. four times a day; Benadryl, 50 mg. four times a day.

Result: On February 1 there were no lesions or wheals, but the left wrist and both palms were still swollen, as were the lips. On February 2 the joints cleared. On February 4 there were recurrent hives on the chin and neck, so another 2,000,000 units of penicillinase were given. On February 11 all symptoms had cleared and the patient was asymptomatic. It was the clinician's opinion that this was "a good result."

Toxicity: None.

Case 25. A 47 year old white male received 600,000 units of depot penicillin twice in one week.

Reaction: Acute erythema and edema of fingers, palms and soles.

Treatment: Only penicillinase was used, 1,000,000 units intramuscularly 48 hours after onset of reaction.

Result: Complete clearing in four days.

Toxicity: None.

(Courtesy Dr. Robert H. Snapp, Phoenix, Arizona.)

Case 26. A 35 year old white male received depot penicillin, 600,000 units intramuscularly daily for six days.

Reaction: Urticaria with severe pruritus of palms and soles.

Treatment: Only penicillinase was used, 1,000,000 units intramuscularly, given six weeks after the penicillin was started and four weeks after onset of the reaction. A second injection of penicillinase, 1,000,000 units intramuscularly, was given one week later.

Result: Ninety-five per cent improvement in one week after first injection.

Toxicity: Pain at site of injection for three days.

(Courtesy Dr. Robert H. Snapp, Phoenix, Arizona.)

Case 27: A 22 year old white male received 1,200,000 units of procaine penicillin intramuscularly.

Reaction: Urticaria and edema of palms, soles, arms and legs, with periorbital edema 10 days after administration of penicillin.

Treatment: Only penicillinase was used, 1,700,000 units intramuscularly, given 48 hours after onset of the reaction.

Results: Partial clearing in 24 hours, complete in 48 hours.

Toxicity: None.

Case 28. A 42 year old white male received a total of 1,200,000 units of depot penicillin in two intramuscular injections given 24 hours apart.

Reaction: Erythema and edema of palms and soles.

Treatment: One million units of penicillinase were given intramuscularly 10 hours following onset of the penicillin reaction.

Result: Complete clearing within 48 hours.

Toxicity: Local pain for 24 hours.

(Courtesy Dr. Robert H. Snapp, Phoenix, Arizona.)

Case 29: A nine year old white male received 1,200,000 units of benzathine penicillin (Bicillin) intramuscularly on February 25, 1957.

Reaction: Giant urticaria, angio-edema especially of soles on March 2, 1957, edema of soles so severe that patient had difficulty in walking.

Treatment: Pyribenzamine, 25 mg. four times a day for five days. However, the condition of the patient's feet worsened, so Neo-cortef was started, 2.5 mg. every eight hours, then every six hours for two days. The reaction continued to become more severe, until the patient was unable to walk. One week after onset of reaction, 1,200,000 units of penicillinase were given intramuscularly.

Result: Partial clearing in 24 hours, complete and dramatic clearing in 48 hours.

Toxicity: None.

Case 30. A 52 year old white female received two "injections" of penicillin intramuscularly.

Reaction: Giant urticaria of arms, face and legs with serum-sickness type of inflamed swelling of the left ankle two weeks after the administration of penicillin.

Treatment: Penicillinase only was used, 1,700,000 units after onset of the reaction.

Result: Urticaria disappeared 24 hours after the use of penicillinase, and the left ankle was much improved; it was completely normal in 48 hours.

Toxicity: Local pain at site of injection for 24 hours; no induration.

(Courtesy Dr. Sam Harper, Madison, Wisconsin.)

Case 31. A 42 year old white male received 400,000 units of procaine penicillin intramuscularly.

Reaction: Giant urticaria, severe and extensive.

Treatment: Penicillinase was given, 1,700,000 units intramuscularly two days after onset of the reaction. One tablet of prednisolone, 2.5 mg., was given before the penicillinase.

Result: Seventy-five per cent clearing in 48 hours, complete clearing in 72 hours. Pruritus was relieved in 24 hours after administration of penicillinase. The clinician states: "I feel the treatment was definitely superior to anything I have used in the past."

Toxicity: None.

(Courtesy Dr. Donald Dieter, Madison, Wisconsin.)

Case 32. A 31 year old white female received two intramuscular injections of procaine penicillin, 600,000 units each. A hematoma formed at the site of the second injection.

Reaction: One to three days after the administration of penicillin, urticaria was noted around the site of the injection and on one arm.

Treatment: Penicillinase only was used, 1,000,000 units intramuscularly six hours after onset of the reaction.

Result: The urticaria cleared within three hours. There was a slight recurrence the following day at the site of the injection, and slight itching there for two days.

Toxicity: Local pain and lemon-sized swelling which lasted 12 hours.

(Courtesy Dr. John Beyers, Madison, Wisconsin.)

Case 33. A 36 year old white female received three intramuscular injections of procaine penicillin, 1,200,000 units each.

Reaction: Urticaria appeared on face, chin, arms, hands and legs nine days after the initial penicillin injection.

Treatment: Only penicillinase was used, 1,700,000 units, started 10 hours after onset of the reaction.

Result: Partial clearing of urticaria in 24 hours, further clearing in 48 hours, and complete clearing in 72 hours.

Toxicity: Moderate local pain and induration lasting 24 hours.

Case 34. A 21 year old white male received three 2 c.c. injections of Combiotic intramuscularly.

Reaction: Generalized giant urticaria with angio-edema of the face and joints, serum-sickness type of arthralgia, with fever, coming on about two weeks after the administration of Combiotic.

Treatment: One million units of penicillinase were given intramuscularly 48 hours after the reaction was noted. The patient also received 20 units ACTH intravenously, with 1,000 c.c. 5% glucose, 25 mg. Phenergan intravenously, Pyribenzamine tablets and adrenalin in oil.

Result: There was an almost complete absence of symptoms and signs in about 24 hours. There was a slight recurrence 12 hours later, but again complete freedom after above symptomatic treatment. "Seems to be 'doing the job' at least in reducing the length of morbidity."

Toxicity: None.

Case 35. A 49 year old white female received Combiotic intramuscularly every 12 hours for eight days.

Reaction: Serum-sickness type with urticaria.

Treatment: One million units of penicillinase intramuscularly were started on the second day of the reaction. The patient also received Sandostene intravenously, and intramuscular ACTH and calcium lactate.

Result: Twenty-four hours after administration of penicillinase the patient had definitely improved. In 48 hours the symptoms had almost disappeared. In 72 hours the patient was symptom-free.

Toxicity: None.

Case 36. A white male received 600,000 units of penicillin intramuscularly.

Reaction: Serum sickness developed, with swollen joints, urticaria and pruritus.

Treatment: "Patient had been given intravenous aminophylline and calcium gluconate for three weeks by another physician. Given 2 c.c. of penicillinase intramuscularly three weeks after the onset of the reaction. Was also given Chlor-trimeton, 12 mg. twice a day, ACTH, 40 units intramuscularly, and Cohydeltra, 5 mg. three times a day for two days."

Result: All joint symptoms and skin lesions had cleared approximately 48 hours after administration of the penicillinase.

Toxicity: None.

Case 37. A 60 year old white male received 600,000 units of procaine penicillin intramuscularly for four injections.

Reaction: Simple urticaria appeared seven days after the last penicillin was administered, and also large welts, of which several had been scratched to the point of bleeding.

Treatment: Only penicillinase was used, 1,700,000 units intramuscularly three days after onset of the reaction.

Result: There was prompt relief of itching, and almost complete clearing in 24 hours. A few small hives reappeared three days after administration of penicillinase, but these were not treated and disappeared spontaneously in two days.

Toxicity: Patient complained of pain at the site of the injection, but there was no induration.

(Courtesy Dr. John Byer, Madison, Wisconsin.)

Case 38. A 35 year old white male received 2 c.c. Duracillin intramuscularly.

Reaction: Nine days later the patient developed marked generalized edema of the entire body, severe itching and erythema, and periorbital edema of such degree that his eyes were swollen shut. There was some respiratory distress indicative of laryngeal edema.

Treatment: Only penicillinase was used, 1,700,000 units given intramuscularly within 24 hours after reaction started.

Result: Four hours later there was improvement in the itching, and 12 hours later the patient could open his eyes. Forty-eight hours after the use of penicillinase the symptoms had completely cleared, and there was no recurrence.

Toxicity: None.

(Courtesy Dr. John F. Moon, Baraboo, Wisconsin.)

Case 39. A 40 year old white male received 400,000 units of penicillin, plus 1 gm. streptomycin on May 18 and 19 intramuscularly.

Reaction: Large hivelike lesions appeared on the hands and feet especially; swollen, red, itchy patches as large as a dollar appeared on May 25.

Treatment: The patient was given 1,700,000 units of penicillinase, and ephedrine, 0.25 gm. three times a day.

Result: Six hours after the administration of penicillinase, the lesions became smaller and looked less irritated.

Toxicity: None.

(Courtesy Dr. John F. Moon, Baraboo, Wisconsin.)

Case 40. A 32 year old white female received 800,000 units of procaine penicillin intramuscularly.

Reaction: Simple urticaria, generalized, moderate.

Treatment: Penicillinase 1,700,000 units intramuscularly, also Benadryl and Chlortrimeton.

Result: Marked clearing within four hours, complete clearing within 12 hours. "We feel penicillinase is very good."

Toxicity: Severe local pain first 12 hours.

(Courtesy Dr. J. L. Dean, Madison, Wisconsin.)

Case 41. A 20 year old white female received 400,000 units of Duracillin with 1 gm. streptomycin intramuscularly at 10 a.m. June 11.

Reaction: By 2 p.m. the patient had urticaria with throat edema to such an extent she could hardly breathe.

Treatment: Obenzoin was used, with very little success. At 4:30 p.m. 1,700,000 units of penicillinase were given intramuscularly.

Result: Three hours after the use of penicillinase the patient's symptoms cleared.

Toxicity: None.

(Courtesy Dr. John F. Moon, Baraboo, Wisconsin.)

Case 42. A 47 year old white female received 800,000 units of procaine penicillin on April 22, 1,200,000 units of procaine penicillin on April 23, and 600,000 units of procaine penicillin plus 600,000 units of Bicillin on April 26 intramuscularly.

Reaction: On April 28 there was the onset of arthritis of the ankles and lower legs, erythema, edema, tenderness and pain.

Treatment: Prednisolone, two courses of six days each; penicillinase, 1,700,000 units intramuscularly and 1,700,000 units intravenously five days after onset; 1,700,000 units five days later; 1,700,000 units after five more days; 1,700,000 units 21 days after that.

Result: There was subjective and objective improvement two days after initial penicillinase injection, complete recovery in 40 days. "Results probably would have been better with earlier institution of penicillinase."

Toxicity: Sore hip after one injection.

(Courtesy Dr. James N. Moore, Madison, Wisconsin.)

Case 43. A 54 year old white male received 2 c.c. Duracillin daily for three days intramuscularly.

Reaction: Generalized urticaria with much swelling of the eyelids and face began on the third day.

Treatment: Penicillinase, 400,000 units, and 1 gm. streptomycin.

Result: Symptoms were greatly relieved in four and one-half hours.

Toxicity: None.

(Courtesy Dr. John F. Moon, Baraboo, Wisconsin.)

Case 44. A 56 year old white female received 600,000 units of Bicillin intramuscularly, and penicillin troches.

Reaction: Simple urticaria appeared two weeks after the injection. There was a marked local reaction to Bicillin for three days.

Treatment: 1,700,000 units of penicillinase given two days after onset. Antihistamines and adrenalin were used initially, but were stopped when penicillinase was given.

Result: Hives disappeared six hours after the use of penicillinase.

Toxicity: There was some local pain at the site of the injection. (The patient was unable to sit down for two days.)

(Courtesy Dr. John Byer, Madison, Wisconsin.)

Case 45. A 45 year old white female was given long- and short-acting penicillin on the same day.

Reaction: Multiple polyarthritis, migratory, with local joint swelling and redness. The symptoms were suppressed with cortisone, but reappeared with discontinuation of the steroid.

Treatment: Penicillinase, 1,700,000 units, was given intramuscularly three days after the onset of the reaction, also prednisolone, 20 mg. off and on, plus one day of interrupted treatment.

Result: The joints became asymptomatic 12 to 14 hours after penicillinase was administered, and there was no recurrence. "Very good response."

Toxicity: Severe local reaction (subjective).

Case 46. An 11 month old white male received 1 c.c. of Salk vaccine (which contains 400 units of penicillin) subcutaneously.

Reaction: There was marked, extensive urticaria with pruritus 10 days after administration of the Salk vaccine. (The child had also received penicillin some months before.)

Treatment: Penicillinase, 1 c.c., was given intramuscularly two weeks after the reaction started. ACTH had been given previously, without effect.

Result: All lesions completely cleared about 12 to 18 hours after the use of penicillinase.

Toxicity: None.

From the response to penicillinase, this was undoubtedly a penicillin reaction, the first I have seen due to penicillin in Salk vaccine. The child's mother apparently has multiple allergies.

Discussion

Basically, all that can be said for penicillinase is that it hydrolyzes and inactivates penicillin. However, if in treating an antigen-antibody reaction one is able to interfere with the reaction by inactivating the antigen with an enzyme, then that treatment can be expected to be sound and effective. The foregoing case reports bear this out.

One cannot expect that removal of the antigen alone will in every case immediately reverse the vascular damage or vasculitis present. Spontaneous

tissue repair in the absence of the antigen will vary from patient to patient. For the purpose of this study, penicillinase was used alone in every case possible. The severe pruritus from the giant urticaria was usually relieved within 24 hours. The fact that most of the patients in this report were completely free of their urticaria and angio-edema within 24 to 72 hours is unusual when compared with previous clinical experience in treatment of penicillin reactions with antihistamines, ACTH, steroids, or all three.

A major clinical achievement of penicillinase would seem to be the absence of recurrence of the reaction to penicillin after the adjuvant use of antihistamines, ACTH or steroids is stopped. However, as noted in some cases (cases 6, 23, 24) in this study, when a patient becomes so saturated with penicillin, especially following multiple injections of benzathine penicillin (Bicillin), the tissue saturation of penicillin may outlast the metabolic destruction of penicillinase. For this reason, multiple injections of penicillinase may be required at four- to five-day intervals, since the average duration of the present penicillinase preparation in the body is four to seven days. No sensitivity reactions to penicillinase after repeated injections have been noted. Theoretically, if penicillinase were not metabolized in the body, a single unit could inactivate penicillin in units approaching infinity.

Analysis of these reports reveals that the better clinical response was noted in patients who were given penicillinase within a few hours to a few days after the onset of the reaction. In contrast, in those cases where the penicillinase was given weeks or months after the reaction started (cases 6, 18, 20, 21) the clinical response was less favorable. It is felt that in these four cases the vasculitis may have become self-perpetuating through the development of auto-antibodies to the patient's own tissue protein breakdown. This is speculative, but it points up the supplementary need for steroids or ACTH along with penicillinase in these longer-term reactions.

No local or systemic reactions were noted in toxicity studies with many guinea pigs, nor in the 20 humans who received penicillinase initially in the in vivo studies [1] and the 46 noted in this report. Occasionally local reactions (case 21) are noted following injections of penicillin itself, or other injectables. One wonders whether these represent local hemorrhage with hematoma formation from the trauma of the injection, rather than a local sensitivity reaction.

A word might be said concerning the use of penicillinase in anaphylactic reactions to penicillin. If a patient dies within a few minutes after a penicillin injection, certainly penicillinase would not have time to help. It is speculative whether deaths occurring within a few minutes after a penicillin injection are true anaphylactic reactions, or whether the particulate procaine penicillin was inadvertently injected intravenously. With anaphylactic reactions that occur an hour or several hours after an injection of penicillin in which the patient develops peripheral vascular collapse, laryngeal edema or asthma, etc., penicillinase may be of great benefit, and may be

given intravenously as well as intramuscularly. With rapid inactivation of the offending antigen, followed by supportive therapy consisting of pressor agents and other means to control the shock, it is felt that many or all of these patients could be salvaged. For this reason, and from these studies, penicillinase should be kept on hand in every doctor's office or hospital where penicillin is administered.

It is suggested that penicillinase is no single injection cure-all for penicillin reactions. The patient with a reaction should initially be given penicillinase and at the same time, or subsequently, depending on the severity of the reaction, be given antihistamines or ACTH or cortical steroids. With the use of penicillinase, the offending antigen is hydrolyzed and the reaction more quickly controlled and less apt to recur.

It is hoped that this study will stimulate the search for other enzymes specific for antigens responsible for the many allergic diseases with which humanity is plagued. As examples, finding an enzyme specific for the substrate of the ragweed pollen protein or an enzyme specific for the beta-hemolytic streptococcus-plasma protein complex of rheumatic fever would be highly desirable.

Summary

Forty-six patients with penicillin reactions were treated with penicillinase. Twenty-four of these patients were treated with intramuscular penicillinase alone, with uniformly good results. The other 22 patients had previously received or were given concomitant therapy with various antihistamines and/or ACTH and steroids. In 20 of these patients the favorable clinical response seemed to be directly attributable to the penicillinase. It is interesting to note that in the two cases with a poor response (case 18 and 20), the penicillinase was given weeks to months after the reaction started. Also, in one case that could be classified as only a fair response (case 21), the penicillinase was given two weeks after the onset of the reaction.

No systemic toxic reactions to single or multiple injections of penicillinase were noted. A few patients complained of pain at the site of injection, and one patient (case 21) had a local reaction with induration which may or may not have been due to the enzyme. No local or systemic toxic effects were noted in the 20 patients and many guinea pigs reported in the initial study.[1]

Penicillinase should prove to be extremely valuable adjuvant therapy in the treatment of penicillin reactions.

Summario in Interlingua

Penicillinase, un enzyma producite per certe bacterios, se ha monstrate capace a hydrolysar, rapidemente e in vivo, penicillina a in acido penicilloic. Iste principio esseva usate clinicamente in le tractamento de patientes con reactiones a penicillina.

Quaranta-sex patientes con reactiones a penicillina esseva tractate con penicillinase purificate in doses de inter 1.000.000 e 2.000.000 unitates per via intramuscular

Vinti-quatro de iste patientes recipeva nulle altere tractamento. Le resultatos esseva uniformemente bon. Le remanente 22 patientes habeva recipite previemente o recipeva concomitantemente varie antihistaminas e/o ACTH e steroides. In 20 del patientes de iste ultime gruppo, le favorabile responsa clinic pareva directemente attribuibile al action del penicillinase. In le duo casos in que le responsa al penicillinase esseva pauco bon, le administration de iste enzyma esseva effectuate septimanas o menses post que le reaction a penicillina habeva comenciate. In un caso, in que le responsa non poteva esser classificate como plus que "satis bon," le administration de penicillinase esseva effectuate duo septimanas post le declaration del reaction.

Nulle reactiones systemic de natura toxic esseva notate post injectiones individual o multiple de penicillinase. Alicunes del patientes se plangeva de dolores in le sito del injection, e un patiente habeva un reaction local con induration, sed il non esseva clar si o non isto esseva causate per le enzyma. Nulle local o systemic effectos toxic esseva notate in le 20 patientes e le grande numero de porcos de India reportate in le studio initial.[1]

Penicillinase va esser recognoscite sin dubita como un adjuvante preciosissime in le tractamento de reactiones a penicillina.

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ACUTE ACQUIRED HEMOLYTIC ANEMIA IN ASSOCIATION WITH ACUTE VIRAL HEPATITIS *

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THE association of anemia with chronic liver disease has been well documented. The type of anemia varies with various reports, which is understandable, since the factors of storage of antianemic factor, increased bleeding tendency, and nutrition as well as increased rate of cell destruction are involved. Whether the increased rate of cell destruction is due to the continuous fractional removal of red blood cells by some process which is localized, or by the continuous production of a rapidly acting hemolysin in amounts which destroy only a portion of the circulating red blood cells, is not known.[1] Jandl demonstrated that Cr^{51}-tagged autogenous red blood cells transfused showed heavy concentration in the spleen and abnormally little in the liver.[1] He also showed that the bone marrow response to the anoxia of the anemia was less than normal in chronic liver disease, suggesting again a nutritional factor.[1]

In 1939 Watson [2] reported eight cases of acquired macrocytic hemolytic anemia in association with chronic liver disease. One of these was in association with "severe prolonged catarrhal jaundice."

Certain authors in the foreign literature have suggested an association of hemolytic anemia with viral hepatitis.[3, 4, 5] However, all have been interested in hemolytic anemia as a sequela and not as a complication of the acute attack.

The occurrence of liver damage in association with hemolytic anemia has been reported.[6, 7, 8, 9] All had repeated episodes of hemolysis. The first case [6] was somewhat complicated by the presence of a streptococcus in the wound. The case of Farrar [7] was cured by splenectomy. Hyman and Southworth [9] reported 21 patients with hemolytic anemia with liver derangement. In eight of these the derangement was proved. Six had splenectomy, without benefit. All had chronic liver disease, or liver disease in association with systemic disease.

The literature on the association of hemolysis with liver disease is totally referable to chronic liver disease. In this paper we are interested only in acute hemolysis of red blood cells in association with acute viral hepatitis. Three cases will be presented which seem to show this association.

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Case Reports

Case 1. History of Present Illness: The patient, a 43 year old white American female of Dutch-English descent, was admitted to the Harrisburg Hospital on April 7, 1955, with a chief complaint of chills and fever. She had experienced generalized weakness for one month, and had spent the week prior to admission in bed because of chills and fever. Anorexia was marked. There was occasional sharp shooting epigastric pain. The urine had been dark and the stools light in color for one week prior to admission.

Past Medical History: The patient had had diphtheria at age 14, removal of a Bartholin's cyst at age 30, and phlebitis of the left leg at age 42. She was gravida II, para II.

The systemic review revealed that the patient used "nerve pills" for sleeping, and experienced "occasional" nosebleeds. She had had labile hypertension since 1947, and had occasional urinary frequency. The patient used alcohol only rarely, and had had a good appetite. The menstrual cycle was normal. The family history was noncontributory. There had been no blood dyscrasias, easy bleeding, anemia or jaundice in the family.

Physical Examination: Blood pressure, 130/80 mm. of Hg; pulse, 80; temperature, 102.4° F. Clinical jaundice was present. There was no remarkable lymphadenopathy, spider nevi, palmar erythema or ecchymoses. The liver was enlarged to 2.0 cm. below the right costal margin in the midclavicular line; the edge was smooth and tender. The spleen was palpable.

Course in Hospital: On admission the patient appeared to be a case of an ordinary hepatocellular jaundice. Her temperature ranged from 99° F. to 101° F. during the first week. She ate well and was comfortable except for generalized itching at night. The liver continued to enlarge, and was four fingerbreadths below the right costal margin on the sixteenth hospital day. By the twenty-third day the spleen was larger, and she was complaining of pain in the epigastrium following meals, and generalized itching. On the twenty-seventh day the temperature spiked to 101.2° F., and the following day to 103.2° F. On May 3 (the twenty-seventh day of illness), she complained of weakness and appeared more jaundiced, but the mucous membranes seemed pale. Her stools had remained light in color and her urine dark. There was no evidence of hemorrhage from any area. A blood count on May 5 showed 1,530,000 red blood cells, with 3.99 gm. of hemoglobin. The patient was given 1,000 c.c. of whole blood, followed by 1,000 c.c. of 10% glucose in water with 100 mg. of hydrocortisone. Tetracycline, 250 mg. every four hours, was given orally. Repeated blood cultures (nine) were sterile. She received 1,000 c.c. of whole blood the following day (May 6), and 500 c.c. daily for the next three days (May 7, 8 and 9). The 10% glucose in water with 100 mg. of hydrocortisone was given daily for the next two days (May 6 and 7), and then cortisone, 25 mg. four times a day, was given orally for three days (May 8, 9 and 10), three times a day for three days (May 11, 12 and 13), and twice a day for 12 days. She was discharged on May 30, 1955, on her fifty-fourth hospital day. She has remained well to date, and had a repair of a rectocele and stripping of varicose veins in June, 1956. At that time the hemoglobin, white blood cells and differential count, thymol turbidity, serum bilirubin, alkaline phosphatase and bromsulfalein (5 mg. 45-minute method) were normal. The cephalin flocculation was 3 plus at 24 and 48 hours.

Laboratory Findings (table 1): The blood count on admission was normal except for a slight leukopenia. The red blood cells and hemoglobin decreased during the illness. On about the twenty-fifth or twenty-sixth hospital day there was a drop to 1,530,000 red blood cells and 3.99 gm. of hemoglobin. The bilirubin was 8.6 mg.% total on admission, and gradually rose to 17.4 mg.% on April 19. By April 25 it had

TABLE 1

1955	4–8	4–11	4–15	4–19	4–25	5–1	5–5	5–6	5–6 P.M.	5–8	5–9	5–12	5–17	5–25
RBC	4.35 M			3.32	3.16		1.53	2.42	2.61	2.71	2.94	3.29	3.94	4.12
Hb.	11.83 gm.			10.57	9.73		3.99	6.3	6.3	7.7	8.82	10.5	12.6	12.39
WBC	3450			4250	4100		2600	6550	14,000	13,850	10,500	5250	5000	5150
Neut.	50%			62	51		64		71	83	74	58	76	61
Lymph.	44			36	41		34		18	17	26	36	21	39
Mono.	6											3		
Bilirubin														
Direct	6.2	9.0	9.8	13.0	3.4	10.8			5.6		3.3	2.4	1.5	1.1
Indirect	2.4	2.6	2.4	4.4	2.2	4.6			2.8		1.3	1.2	1.6	0.8
Total	8.6	11.6	12.2	17.4	5.6	15.4			8.4		4.6	3.6	3.1	1.9
Alk. phos.	8.5 BU	7.8 BU	7.4 BU	8.6	8.6	7.5								
Ceph. flocc.														
24 hr.	3+				4+									
48 hr.	4+				4+									
Serum alb.					3.34									
Serum glob.					3.61									
Prothrombin					18.9 sec.			16.9						
Control					13.3 sec.			15.0						
Chol.						311								
Chol. ester						79								
Heterophil						Neg.	Neg.							
Fragility														
Starts									.40					
Ends									.28					
BUN									9.4					
Coombs,														
Direct									Neg.					
Indirect									Neg.					
Brom.														10%

decreased to 5.6 mg.%. On May 1 it had risen to 15.4 mg.%, and the patient was clinically more jaundiced. Pallor was noted the following day, and two days later the low blood count. The remainder of the laboratory studies were confirmatory of hepatocellular disease, with elevated cephalin flocculation, decreased prothrombin activity, low cholesterol esters and slightly elevated alkaline phosphatase. The Coombs' test, heterophil antibody and red cell osmotic fragility test were normal.

Specific Laboratory Procedures: The heterophil antibody was negative on two occasions. Serologic tests for auto-agglutination, iso-agglutination, isohemolysis, autohemolysis and repeated direct and indirect Coombs' tests at 37° C. were negative. A direct Coombs' test at 4° C. was not performed. A cold auto-agglutinin was found in a titer of 1:32. This was interpreted as compatible with a viral infection and not as definite evidence of any red blood cell sensitization. All blood cultures were negative.

Discussion: From both the clinical and the laboratory standpoint this case was hepatocellular jaundice, probably of viral origin. On about the twenty-fifth or twenty-sixth day of hospitalization something acute happened, characterized by an elevated temperature, weakness, increase in clinical jaundice, paleness of the mucous membranes, and associated with an increase in size of the spleen. The laboratory studies showed an increase of the serum bilirubin, which represented a reversal of the bilirubin trend, and a marked drop in the red blood cells and hemoglobin. The marked initial leukopenia, with a leukocytosis the following day, is intriguing.

There was no evidence of external blood loss. There was no reason for the bone marrow suddenly to stop production, although the leukopenia might suggest an aregenerative bone marrow crisis, but the rapid recovery would be against this concept. The process most likely involved was an intravascular hemolysis, as suggested by the rising bilirubin and the rapid response to therapy. The therapy was aimed at replacement of red blood cells and control of hemolysis. This was accomplished by whole blood transfusions and intravenous hydrocortisone.

Case 2. History of Present Illness: The patient, an 11 year old white American boy of English descent admitted to the Harrisburg Polyclinic Hospital on January 19, 1955, had been well until January 12, when he developed malaise, headaches and a slight fever. His family physician found a fever of 101° F., diagnosed "grippe" and treated him with "fever pills." On January 13 the temperature was 103.6° F., and penicillin was given parenterally. Anorexia was prominent, but the patient seemed clinically better on January 14. On January 15 the urine became dark, and clinical icterus was noted. The patient experienced epigastric pain, and vomited recently eaten food. Jaundice increased, and anorexia persisted on January 16 and 17. On January 18 he received more parenteral medication. The jaundice had increased markedly, the right upper quadrant pain had become more severe, and his general condition had worsened.

The patient had had contact with many jaundiced children in school. He had had no parenteral injections for the year prior to his illness, and had been taking no medications. The family history and past medical history were noncontributory.

Physical Examination: Temperature, 102° F. The patient was markedly jaundiced and lethargic but could be aroused. There was extreme right upper quadrant tenderness, with guarding, with suggestion of liver enlargement, down four finger-breadths in the midclavicular line. There was no splenomegaly.

Laboratory Findings (table 2): The red blood cell count on admission was 2,440,000; hemoglobin, 7.3 gm.%; marked leukocytosis; 10% metamyelocytes; 1% myelocytes; 15% normoblasts. Two days later there was an 11.2% reticulocyte count, and the leukocytosis had decreased. The bilirubin on admission was 30 mg.%; on January 22 it was 62.5 mg.%. It then fell rapidly until February 1, when the decline became gradual. The remainder of the laboratory findings suggested hepatocellular jaundice with elevated thymol turbidity, prolonged prothrombin time and low cholesterol. The Coombs' test and heterophil antibody test were normal.

Course in Hospital: The patient on admission was markedly ill, deeply jaundiced, anorexic, nauseated and lethargic. He was treated on admission with 10% glucose in N/2 saline, which was changed to water after 500 c.c.; intravenous Terramycin, 100 mg. per 500 c.c.; 1 c.c. of Solu-zyme per 500 c.c., and intramuscular Terramycin, 50 mg. every 12 hours. On January 20 he was given 500 c.c. of whole blood and

TABLE 2

Laboratory Findings, Case 2

1955	1–19	1–21	1–22	1–24	1–29	2–1	2–5	2–13
RBC	2.44 M	3.32	4.62	4.0	4.19		4.8	4.1
Hb.	7.3 gm.	10.8	14.8	12.4	13.4		14.5	12.8
WBC	25,300	14,700	18,100	10,600	6100		12,700	10,400
Adult forms	50%	79	85	66	36		59	69
Stab. forms	18%	4						
Metamyelocytes	10%	2						
Myelocytes	1%							
Lymphocytes	21%	15	15	30	64		41	31
Eosinophils				4				
Normoblasts	15%							
Reticulocytes		11.2						
Thymol units	37							
Bilirubin (immediate)	30		62.5	17.5	7.5	3.75	3.5	2.0
Alk. phos. (K.A. units)	43							
Cholesterol	119							
Prothrombin								
Control	14.9 sec.							
Specimen	33.4 sec.							
Urine urobilinogen	Neg.							
Platelets		280,000						
Coombs'								
Direct	Neg.							
Indirect	Neg.							
Heterophil						Neg.		

2,000 c.c. of 10% glucose with 4 c.c. of Solu-zyme, 100 mg. of hydrocortisone, and 200 mg. of Terramycin. On January 21 he received 500 c.c. of whole blood and 2,000 c.c. of 10% glucose in water, with 4 c.c. of Solu-zyme and 200 mg. of Terramycin. On January 22, 23 and 24 he received 1,000 c.c. of 10% glucose in water, with 2 c.c. of Solu-zyme and 200 mg. of Terramycin. On January 25 he was given a full diet and Terramycin, 250 mg. three times a day orally. He continued to improve, with an increase in appetite and a decrease in nausea and liver size. He was discharged on February 15, 1955.

Discussion: This boy had a definite change in his condition on the sixth day of his illness. He was sent immediately to the hospital, where the marked anemia with evidence of a regenerating marrow was found. There was no evidence of any external blood loss. The markedly high

serum bilirubin suggests bilirubin of hemolysis added to bilirubin of hepatitis. This bilirubin dropped rapidly. The patient responded to the treatment prescribed. Intravenous hydrocortisone was used only following the first transfusion. The response of the red blood cells and hemoglobin to this transfusion would suggest that these transfused cells were not hemolysed. The spleen was not palpable at any time. The recovery was complete, and the patient has remained well to date.

Case 3. History of Illness: The patient, a 14 year old white American girl of German descent admitted to the Harrisburg Polyclinic Hospital on October 1, 1956, had as her chief complaints jaundice, weakness, loss of appetite and drowsiness. She had been well until two weeks prior to her admission, when she had begun to have weakness and anorexia. She was seen by her local physician, who prescribed vitamin pills. Ten days prior to admission she first noted jaundice, which seemed to be most marked around the neck and face and was associated with a change in color of the urine. The jaundice persisted unchanged until four days prior to her admission, when it became noticeably more pronounced.

For the first 10 days of her illness the patient had taken adequate amounts of fluids, but for the four days prior to admission her intake had decreased markedly. During the 24 hours prior to admission she became progressively more lethargic and began vomiting. She had passed urine last about 12 hours prior to her admission. The urine was described as initially dark brown in color and then as becoming dark green, and for the four days prior to admission was described as dark red-orange in color. The stools had been dark brown throughout the illness. The patient's only pain was epigastric pain associated with vomiting. She had had no elevation of temperature except for the four days prior to admission, when it was 101° F. She had had no similar attacks prior to the present illness, and had not been exposed to any jaundiced persons. She had received no injections and no transfusions. There had been no contacts with hepatotoxic substances. She had been on a diet for six months and had lost 30 pounds.

The family history was not obtainable, as this child had been separated from her family and had lived with foster parents. The past medical history was noncontributory.

Physical Examination: Blood pressure, 110/70 mm. of Hg; temperature 99° F. rectally; pulse, 88; respiration, 20. The patient was deeply jaundiced. There was no evidence of spider nevi, palmar erythema or ecchymoses. The abdomen was somewhat obese and difficult to examine, but liver and spleen were not palpable. There was some slight tenderness on deep palpation in the right upper quadrant. The patient was markedly lethargic but could be aroused and, when aroused, could answer questions.

Laboratory Findings (table 3): The admitting blood count showed 1,150,000 red blood cells, with 5.6 gm. of hemoglobin. There was a moderate leukocytosis. The reticulocyte count was 7.5. The thymol turbidity and cephalin flocculation were positive. The cholesterol esters were 0, the prothrombin time was markedly prolonged, the serum bilirubin was 50 mg.% total, and reached 75 mg.% on October 4. The urea nitrogen on admission was 136 mg.%, and was 200 mg.% on October 4. The CO_2 combining power was 20.2 mM on admission and dropped to 5.6 mM on October 4.

Treatment: The patient was given 1,200 c.c. of N/3 NaCl with 5% glucose over the first 14 hours. Intensive treatment was then started, with whole blood to replace the circulating blood volume, glucose and vitamin B to support the liver, and antibiotics to control intestinal bacteria. The history of decreased urinary output was thought to have been caused by dehydration, but the azotemia and the low urinary

output after 2,500 c.c. of intravenous fluid suggested a renal shut-down. It was thought necessary to reduce the fluid intake, and this was reduced less than was intended because of an error in calculating the drop per minute of flow rate. The rising blood urea nitrogen and falling CO_2 combining power suggested the use of lactate.

Course in Hospital: Within six hours of admission the patient went into coma from which she never recovered. She lost all contact with surroundings and went into periods of unintelligible and irrational talking and moaning. Tremors were not remarkable. There was no evidence of spontaneous bleeding until the last 12 hours, when she regurgitated coffee-ground material and expectorated blood-stained mucus. She also passed some red blood by rectum and/or vagina at this time. She died at 8:50 p.m. on October 4, 1956.

TABLE 3

Laboratory Studies, Case 3

	10-2-56	10-3-56	10-4-56 a.m.	10-4-56 p.m.
RBC	1.15	3.8	3.84	3.3
Hemoglobin	5.6	12	11.3	10.0
WBC	20,950	13,600	24,600	
Neut.	74	67	74	
Lymph.	26	33	20	
Reticulocytes	7.5			
Bilirubin	50 mg.%		75	
BUN	136 mg.%		200	
Alb.	3.0 gm.%			
Glob.	3.0 gm.%			
Chol.	111 mg.%			
Esters	0			
Thymol	14 units			
Ceph.	4 + 48 hr.			
Prothrombin	66.9 sec.			
Control	13.2 sec.			
Na	135.5 mEq./L.	130.5	129	
K	3.5 mEq./L.	3.25	4.45	
Cl	90.6 mEq./L.	91.2	89.4	90.6
CO_2	20.2 mM	16.6	11.7	5.6
Ca		5.3		
P		5.6		
Heterophil	1.56			
Coombs'	Neg.			
Blood type	B Rh Neg.			

Autopsy Findings: Gross: The body was 64 inches in length and weighed 140 pounds. There were marked icterus and evidence of bleeding from the nose and mouth. The heart weighed 260 gm. The tracheobronchi were filled with mucosanguineous material, and there were scattered areas of atelectasis and congestion. The spleen weighed 420 gm.; it was dark purplish in color, markedly engorged. The liver weighed 1,400 gm.; it was nodular and firm, and a deep tan in color, with scattered nodules of slightly lighter color. There was no congestion or hemorrhage, and no evidence of obstruction to the extrahepatic ducts. The pancreas was normal in appearance. The adrenals weighed 17 gm. The corticomedullary ratio was maintained. The esophagus contained mucosanguineous material. The stomach contained 300 to 400 c.c. of broken down blood. The mucosa showed hemorrhagic gastritis. The small bowel was hyperemic throughout. The right kidney weighed 213 gm., the left, 212 gm. They were brownish green in color and soft to palpation. Their appearance was compatible with cholemic nephrosis. On cross-section the tissues were congested and friable. There was no evidence of hemorrhage.

The musculoskeletal and lymphatic systems were normal. Central nervous system: The brain was congested and edematous. The spinal fluid was icteric. There was no evidence of hemorrhage.

On microscopic examination: The left ventricular myocardium showed a fibrotic epicardium with infiltrations of lymphocytes and mononuclear cells. Both lungs showed large foci in which the alveolar spaces were dilated and filled with blood. Other sections showed diffuse infiltrations with lymphocytes, mononuclear cells and occasional neutrophilic granulocytes. The pancreas showed no abnormalities. In the adrenals there was some reduction of cytoplasmic vacuolation in most of the cells throughout the cortices. Pituitary sections were normal. The stomach mucosa was partially intact, with other zones showing hemorrhage. In some regions the gastric mucosa showed a peculiar ectopic squamous metaplasia. The sinusoids of the spleen throughout the red pulp were markedly dilated with associated diffuse and focal hemorrhages. Most of the reticuloendothelial cells throughout the sinusoids showed evidence of phagocytosis of the red blood cells. Other sections showed considerable fine granular brown pigment within many of the macrophages.

Most of the liver sections showed considerable distortion of the usual architectural pattern with rather marked fibrosis in the periportal region. Other sections showed extensive nodular regeneration, with bizarre hepatic lobules and displaced central veins. In most regions the periportal fibrosis was associated with diffuse infiltrations of lymphocytes and mononuclear cells. There was considerable bile duct proliferation of the smaller intracanalicular bile channels. Other sections showed marked degenerative changes of the individual cells within the hepatic lobules. Most of these showed extreme cytoplasmic vacuolations and contained moderate amounts of fine, golden brown pigment resembling bile.

Both kidneys showed extensive degeneration of the proximal and distal convoluted tubules, characterized by marked vacuolation of the lining epithelium. Most of the tubules showed atrophy as well as distention with large amounts of amorphous golden brown pigment. Most of the glomeruli showed edema and a deposition of fibrillary material within Bowman's space.

The periportal lymph nodes showed a diffuse interstitial fibrosis with marked erythrophagocytosis throughout the sinusoids, as well as a slight eosinophilia.

Central nervous system, ovaries, uterus and urinary bladder: Normal.

Discussion: From the necropsy findings of the hard, fibrotic, nodular liver one must assume this girl had preëxisting liver disease. For some reason there was a sudden death of large numbers of liver cells. Certainly one of the possibilities of this added insult was a viral infection, since no other cause, such as a hepatotoxic substance, could be found.

The histologic findings of intensive erythrophagocytosis by reticuloendothelial cells in both lymph nodes and spleen are suggestive evidence of increased red blood cell destruction. The brown pigment in the macrophages from the splenic sinusoids is suggestive of the same phenomenon.

Twenty-four hours prior to admission this patient became worse. She was unable to retain food or liquids, had a decreased urinary output, and became more lethargic and more jaundiced. On admission the low blood count suggested a loss of red blood cells, and since there was no evidence of extravascular loss, it was assumed that it was intravascular. The leukocytosis and reticulocytosis suggested a functioning bone marrow. That this was a hemolysis was also suggested by the markedly elevated bilirubin (50 mg.%). This would suggest that the bilirubin of hepatocellular disease

was added to that of the hemolysis. The marked decrease in urinary excretion of bilirubin because of the renal shutdown probably contributed to the final reading of 75 mg.% of serum bilirubin.

This case was complicated by the renal shutdown, which was reflected in the rising blood urea nitrogen, decreased urinary excretion and falling CO_2 combining power. The reason for this renal failure is not known. There was no evidence of preëxisting renal disease. The renal failure seriously limited therapeutics. However, the amount of hepatocellular damage was so marked and so complete that it is questionable if this patient would have recovered even with normally functioning kidneys. It was of interest that the marked liver cell damage was mostly confined to the original liver cells and not to those in the regenerating nodules.

Comments

It would appear that the anemia in these cases was hemolytic. The problem, then, is to explore the possible reasons for the hemolysis and their relationship to acute liver disease.

The first factor to consider is the fragility of the red blood cell in infectious hepatitis. Havens [10] and McCarty [11] report normal osmotic fragility. Finks and Blumberg,[12] Bohr [13] and Cohen [14] report increased resistance. Bornemann and Michel [15] report an increased spherocyte index in 12 out of 40 cases of epidemic hepatitis studied. Of these 12, one showed a positive Coombs' test, all had increased thickness and volume of the red blood cells, all had decreased resistance of the red blood cells following incubation, seven had decreased resistance before incubation, eight had increased reticulocytosis. It would appear that there is no uniformity of opinion concerning the osmotic resistance of the red blood cells in infectious hepatitis.

The possibility as to whether the virus itself might alter the resistance of human red blood cells to hemolysis must be considered in view of certain experiments.[16, 17, 18] This might suggest that the hemolysis reflects the severity of the attack and the initial viral load. Two of the patients were severely ill early in the course of the disease, whereas the other was quite ill at the time of her hemolysis. We assumed this latter case was more severely ill due to the hemolysis, but it could be that the exacerbation of the illness produced the hemolysis.

The next factor to consider is the abnormal destruction of the red blood cells by some organ. This could be a factor in chronic liver disease with associated splenomegaly, but it is more difficult to apply to acute hemolysis in acute liver disease. However, case 1 had a splenomegaly which clinically seemed to change in size. Case 3 had a splenomegaly which could have been due to chronic liver disease. The histologic findings of the marked erythrophagocytosis by the reticuloendothelial cells of the spleen, as well as the finding of brown pigment in the macrophages of the splenic sinusoids, are evidence that the spleen played a part in the hemolytic phenomena in this case. An acute splenomegaly has been reported in 15 to 25% of cases of infectious

hepatitis. The possibility that an acute splenomegaly has the same hypersplenism potentialities as chronic splenomegaly must be considered.

Another factor is the destruction of the red blood cells by some hemolysin. This could be due to a sensitization of the red blood cells by some abnormal globulin.[19] Abnormal globulins are usually thought of in association with chronic liver disease. In all three of these cases the Coombs' test was negative.

The possibility of the circulation of hematotoxic substances of endogenous origin due to impairment of the liver's detoxifying properties must be considered.[19] That such hematotoxic substances might arise from liver cell breakdown itself is suggested by Tyler,[20] who from fetal guinea pig liver was able to separate, by ultracentrifugation, a lytic and inhibitor substance. This lytic substance will lyse the red blood cells of the mother guinea pig and of the rat. It was suggested that this factor was an enzyme because of its reaction to heat and to certain enzyme poisons. It was also shown that in the adult guinea pig liver, the inhibitor substance is more prominent. One wonders if such substances are present in human livers and are in such balance that they are compatible with the full normal life span of the red blood cells, but that sudden severe hepatocellular damage upsets this balance and hemolysis occurs.

Summary

Three cases with acute acquired hemolytic anemia in association with apparent acute viral hepatitis are presented. The possible mechanisms of this hemolytic process are discussed.

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Summario in Interlingua

Es reportate tres casos de acute hepatitis virusal associate con acute hemolyse del erythrocytos. Le patientes esseva un femina american de racia blanc de 43 annos de etate, un puero american de racia blanc de 11 annos de etate, e un puera american de racia blanc de 14 annos de etate. Omnes esseva marcatemente malade. In un, le hemolyse occurreva le vinti-quinte die del maladia; in le altere duo, illo occurreva in le prime phases del maladia. In omnes, le hemolyse esseva characterisate per un rapide reduction del numeration de erythrocytos circulante sin indicios de hemorrhagia o depression functional del medulla ossee, de elevation del numeration leucocytic e reticulocytic, e de elevation del nivello de bilirubina. Le examine physic revelava un approfundamento del jalnessa e un pejoration del stato clinic del patiente. Splenomegalia esseva presente in duo casos. Un del patientes moriva (le puera de 14 annos de etate), e le necropsia revelava pre-existentia de morbo hepatic (con, apparentemente, ingraffation de acute lesiones hepatic), evidentia de phagocytose erythrocytic in splen e nodos lymphatic, e grados marcate de lesion renal. Disruption del functiones renal complicava iste caso. Omne le casos esseva tractate con hydrocortisona intravenose, sed il es difficile evalutar le efficacia de iste agente.

Le factores possibilemente responsabile pro iste acute hemolyse in acute hepatitis virusal es (1) alteration del fragilitate erythrocytic, ben que un revista del litteratura revela differentias de opinion con respecto a iste question, (2) le capacitate del virus mesme de alterar le resistentia del erythrocytos human, reflectente possibilemente le severitate del attacco e le fortia del invasion initial de virus, (3) destruction anormal de erythrocytos per le un o le altere organo, suggerente le possibilitate de hypersplenismo, specialmente in le duo del casos in que splenomegalia esseva constatate, (4) destruction del erythrocytos per un hemolysina, per exemplo in le forma de un globulina anormal que effectua un sensibilisation del erythrocytos, e (5) le possibilitate del presentia de un substantia hematotoxic de origine endogene que esserea, sub conditiones normal, distoxificate per le hepate sed que, a causa del anormalitate del hepate, continua circular. Le qual de iste factores predominava o si il se tractava de un combination de plures de illos non es cognoscite.

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MASSIVE DOSES OF CORTISONE IN HEPATIC COMA*

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HEPATIC coma is a frequent terminal occurrence in advanced atrophic or postnecrotic cirrhosis. Coma can be precipitated in patients with preexisting liver damage by hepatotoxic agents, infection, physical overactivity, improper use of sedatives or narcotics, inadequate diet, trauma or surgery.

Hepatic coma carries with it a high mortality. Murphy[1] in his series of 42 cases had 40 deaths. Snell,[2] in a series of cases reported from the Mayo Clinic, showed that 23 out of 54 cases of atrophic cirrhosis died in coma. Karl et al.,[3] in a review of 58 cases of hepatic coma selected from the records of the St. Louis Hospital, reported that all of the cases in hepatic coma died. Because of the high mortality associated with hepatic coma, many therapeutic regimens have been tried. The usual supportive measures have been used, such as maintenance of fluid and electrolytic balance, correction of anemia, control of infection, antibiotics, intravenous glucose, vitamins, tube feeding and general nursing care. Many drugs have been tried. Human serum has been used with some success, notably in the cases reported by Post.[4] Aureomycin, Tetracyn and Terramycin in large doses have been administered and reports have appeared in the literature which indicate that these drugs may be of benefit.[5]

The steroids have had a great vogue in the treatment of liver diseases. Many articles have appeared concerning their use in hepatitis and cirrhosis of the liver. Results to date have been controversial: some investigators have found them to be of distinct benefit, while others have found their use limited or disadvantageous. Sklar and Young[6] treated 10 patients in hepatic coma with ACTH or cortisone, or both, and found no significant alteration in the downward course of any patient. Five of the patients in coma failed to evidence any change in their status, and the other five, who were in a precomatose state, lapsed into coma. All 10 died. In a recent panel discussion on hepatitis and cirrhosis of the liver, opinion was divided as to the usefulness of ACTH or cortisone.[7] Ducci and Katz[8] reported two cases of hepatic coma as a result of severe hepatitis, both of whom recovered after administration of ACTH. In none of the articles reported to date were *massive* doses of cortisone or ACTH employed. This paper concerns itself with the use of very large doses of steroids in the treatment of hepatic coma resulting from atrophic cirrhosis.

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Materials and Methods

Six patients admitted to Queens General Hospital in hepatic coma resulting from advanced portal cirrhosis were treated with cortisone. Some of these patients relapsed into coma and were treated again. In all, 10 episodes of hepatic coma were treated. The regimen employed was as follows: 250 mg. of cortisone every six hours for from one and a half to two days; then 250 mg. every 12 hours for from one to two days; then 250 mg. daily for from one to two days. The drug was then discontinued. In addition to the cortisone, each patient received such supportive therapy as 5% intravenous glucose, electrolytes as needed, vitamins, blood (if bleeding), and antibiotics. In addition, all patients were given 3 to 6 gm. of potassium chloride daily, either by mouth or intravenously; the exact amount depended on serum potassium levels.

Results

All six patients in this group of cases died. However, the prompt response to massive steroid therapy was striking and warrants reporting. Normally, patients who die in hepatic coma do so without regaining consciousness. In the few who respond to therapy, days usually elapse before the patient becomes responsive. In our series of cases, following 12 to 24 hours of therapy, all but one were alert, coherent, active and able to take nourishment by mouth. In two instances of relapse into coma, the same uniformly good results were obtained after therapy was reinstituted.

It is felt that the reason the patients in this series of cases failed to maintain their improvement was that they were all in an advanced state of hepatic failure. This was borne out by physical examination and liver function tests which showed marked hepatic impairment. Of the six cases treated, two died as a result of gastrointestinal bleeding and in a third (case 5) bleeding was considered the probable cause. Anemia and electrolytic imbalance in one case were considered major factors in the fatal issue. One died due to pulmonary edema, and one in hepatic coma without any response at all. However, the last named patient died eight hours following the start of steroid therapy, hence without adequate therapeutic trial.

No change was noted in the tests for serum cephalin flocculation, thymol turbidity, cholesterol, cholesterol esters, total protein, albumin, globulin and bilirubin, nor in the degree of retention of bromsulphalein. These values remained the same prior to, during and following cortisone therapy. This is in contrast to the results obtained by other investigators, who have found that there was a rise in cholesterol and cholesterol esters, and improvement in the bromsulphalein retention, cephalin flocculation, thymol turbidity, bilirubin and total protein, with a reversal towards normal of the A/G ratio.[9, 10]

In our series of cases there was no demonstrable change in the blood sodium level; on the dosage of cortisone employed, it remained essentially unchanged. However, blood potassium tended to drop. This was cor-

rected by the administration of potassium, 3 to 6 gm. of KCl by mouth each day.

Case Reports

Case 1. A 61 year old Negro female was admitted to the Queens General Hospital for the first time on July 28, 1954, with the chief complaint of jaundice and swelling of the legs since November, 1953. In April, 1954, the patient had developed pruritus and anorexia with nausea and vomiting. She was treated with digitalis and ammonium chloride, with fair results. For many years she had consumed 2 quarts of beer a day, with little or no food.

Physical examination revealed a well developed Negro female who was icteric and had a peculiar, grayish tint to the skin. Temperature was 100° F.; pulse, 108; respiration, 20; blood pressure, 140/90 mm. of Hg. The fundi showed grade 3 retinopathy. The heart was enlarged, and there was a soft systolic murmur at the apex. Subcrepitant râles were heard at both lung bases posteriorly. The liver was palpated 8 cm. below the right costal margin, and had a sharp, nontender edge. A fluid wave and shifting dullness were present, but no spleen or other masses were noted. There was 1 plus sacral and ankle edema. The diagnoses on admission were: (1) hypertensive cardiovascular disease with enlarged heart, congestive failure; (2) Laennec's cirrhosis, decompensated, with jaundice and ascites; (3) questionable hemochromatosis; (4) anemia.

The venous pressure taken on admission was 290 mm. of saline; circulation time, arm to lung, was 11 sec. The patient was treated with vitamins, a high carbohydrate, high protein, low salt diet, digitalis and Mercuhydrin. X-ray of the chest on July 28, 1954, revealed clear lung fields and an enlarged heart. A gastrointestinal series on August 5 and again on October 5, 1954, revealed no esophageal varices. An electrocardiogram revealed digitalis effect and left ventricular hypertrophy. A glucose tolerance test was normal. Urea clearance on September 1, 1954, showed 44% of normal. Skin biopsy, stained for iron, revealed none. Shortly after admission the patient developed urethral bleeding and passed black stools. At the same time ecchymotic areas in the skin were noted. After being relatively well for about six weeks the patient gradually became lethargic, with coarse tremors of the extremities.

Case 1

Date	Na	K	Cl	CO_2	BUN	Creat.
8-3	139	2.5	97		13	
8-5	136	3.4	96	57		
8-19	142	4.0	106	58		
8-26	140	3.9	96		17	
8-27					12	
8-30	136	4.9	97	56		
9-14	143	4.6	102			
9-16	147	5.4	106			
9-22	133	5.8	96	54		
9-24	140	4.7	102	58		
9-27	138	4.9	103	58		
9-29	148	3.8	109	56		
10-1	143	4.6	114			
10-4	145		112	54	51	
10-6	143	3.7	93	56		
10-8	143	3.8	102	54		
10-14	137	5.0	97	60		
10-18	137	5.4	116	58		
10-19	135	4.9	100	57		
10-20	139	5.5	102		60	2.6

CASE 1

Date	WBC	Hg.	RBC	Ht.	P.T.	Chol./ Est.	A/G	Alk. Phos.	C.F.	T.T.	Tot. Bil.
1954											
7-29	7.4	5.2									
8-3				21		173/107	2.1/4.4	5.3	4+	15.5	2.7
8-5	12.0	5.4			21						
8-6		5.5	2.3								
8-12					16	193/123	2.4/4.4	8.7	4+	15.8	2.6
8-17	9.7	6.5	2.7		21						
8-19						208/143	2.4/4.5	4.7	4+	16.2	4.3
8-23	6.9	6.5		25							
8-25					20	165/115	2.2/4.1	6.1	4+	16.1	2.5
8-27	8.2	8.5		30							
8-31					20	225/152	2.2/4.6	7.6	4+	19.3	2.6
9-7					21	212/150	2.6/3.8	6.9	4+		2.4
9-8	7.2	8	2.4								
9-9					19	187/131	6.2	9.4	4+	17.3	2.2
9-14	9.6	7			20	200/129	3.6/2.9	1.8	3+	6.8	1.4
9-22						270/172	2.6/3.9	9.3	4+	16.1	2.5
9-27	13.4	9.5			20	265/164	2.9/3.6	8.1	4+	17.2	3.8
9-30						249/153	2.5/3.3	6.4	4+	16.1	4.3
10-4					20				4+	20.6	
10-14						97/17	2.3/3.0	10.5	4+	16.4	2.5
10-18					22			5.1	4+	18.2	2.6

Urine 8/4/54—Many RBCs.

Platelet count, 172,000; clotting time (Lee & White), 6 min.; no sickle cells. Spinal fluid normal.

On September 16 she was in an "agitated" comatose state. On the same day she received cortisone, 200 mg. every eight hours, with gradual lessening of the comatose state, so that on September 20, 1954, the dose was decreased to 100 mg. every eight hours. This was further decreased to 50 mg. every eight hours on September 21, and to 25 mg. on September 22. On September 24 the cortisone was discontinued. The patient remained well for approximately four days and then lethargy, stupor and tremors reappeared, with a relapse into coma on September 30, 1954. Cortisone was again instituted, the patient receiving 250 mg. every eight hours. On October 1 she was awake, oriented, alert and able to take nourishment by herself. The dosage of cortisone was decreased to 250 mg. twice a day on October 2 and to 100 mg. every eight hours on October 3. Cortisone was discontinued on October 5, 1954. On October 7 the patient again lapsed into coma, and again was given cortisone, 250 mg. every six hours. On October 8 she was awake and confused, but was able to take fluids by mouth. On this date the cortisone was given every eight instead of every six hours. On October 10 the cortisone was given twice a day, and it was finally stopped on October 13, 1954. The patient did well from October 13 to October 20, when she suddenly lapsed into unconsciousness and died within a few hours.

At autopsy the body was that of a well developed, well nourished female weighing about 180 pounds. The liver weighed 1,300 gm.; spleen, 200 gm., and heart, 500 gm. The lungs were moderately emphysematous. Both ventricles of the heart were hypertrophied but not dilated. Examination of the esophagus revealed no gross evidence of varices. Two ulcers were noted in the proximal part of the stomach. The stomach and intestines contained about 2.5 quarts of fresh and partly digested blood. The cut surface of the liver was irregularly granular and corrugated, cutting with a hard and gritty sensation. Fibrous tissue was seen to have distorted the normal lobular architecture. Three gall-stones were found in the gall-bladder. The

spleen had a thickened capsule, with firm parenchyma. The urinary bladder showed some ulcerated and hemorrhagic areas. The adrenals were very small and flat.

Microscopic examination: "There is extensive development of fibrous tissue growing in bundles and strands, crisscrossing the liver parenchyma, irrespective of original lobular architecture, thus forming pseudo-lobules, many of the latter without central veins, others with eccentric intralobular veins. There are areas of bile duct proliferation, some of which are still uncanalized. Periportal round cell infiltration is found. Liver cells show well stained nuclei and cytoplasm."

Adrenal gland tissue beneath the liver capsule was an incidental finding. This showed three well differentiated layers (glomerulosa, fasciculata and reticularis).

Case 2. A 45 year old white female was admitted for the first time to Queens General Hospital on November 10, 1951, because of nosebleeds and hematemesis. The patient had been consuming one to two quarts of beer and wine three or four times a week for 10 to 15 years prior to admission. During this period of time her diet had been poor. In spite of this she had never been ill until one day prior to admission, when she developed a headache followed by a nosebleed, and at the same time passed bright red blood by rectum. Physical examination on admission revealed the following: pulse, 132; blood pressure, 142/80 mm. of Hg; respiration, 24; temperature, 98.6° F. There were numerous spider angiomata over the face, chest and back. There were many ecchymotic areas scattered over the trunk and extremities; there was nonpitting edema of both extremities. There were tarry stools in the rectum. Treatment on this admission consisted of high protein, high carbohydrate, moderate fat diet and vitamins. On this regimen the patient improved and was discharged. She did well following discharge until May, 1953, when she noted the onset of anorexia associated with chills, nausea and jaundice. She became increasingly lethargic. The lethargy progressed to a semicoma, and because of this she was re-admitted on May 27, 1953. Physical examination revealed the following: respiration, 24; pulse, 96; blood pressure, 140/80 mm. of Hg; temperature 99° F. The patient was grunting, groaning and disoriented; the sclerae were icteric, the skin had a bronze color. Four plus leg edema which extended up to the thighs was noted. On this admission the diagnosis of Laennec's cirrhosis with hepatic coma was made. On May 27, 1953, cortisone was started. The patient received 300 mg. of cortisone, then 50 mg. every six hours until June 1, 1953, when the dosage was changed to 50 mg. three times a day until June 6, 1953, when it was stopped. The day following the administration of cortisone therapy the patient was clinically alert, rational and able to take nourishment by mouth. In addition to the cortisone the patient received antibiotics and vitamins. She was discharged greatly improved on June 18, 1953, although she was still icteric at that time. Following discharge she did well until 14 days prior to her third admission, on May 1, 1954, when she noted a recurrence of her leg edema, ascites and shortness of breath. Four days before admission she noted bloody diarrhea. During the days prior to admission her temperature fluctuated between 101° and 104° F. On admission physical examination revealed a blood pressure of 165/45 to 130/70 mm. of Hg; respiration, 26; pulse, 120. The patient was icteric. The liver was palpated one fingerbreadth below the right costal margin. There was 4 plus pitting edema of both legs, with cellulitis and ecchymosis at injection site. The patient was treated with penicillin, ammonium chloride, Mercuhydrin, digitalis and vitamins, with an apparently good response, and was discharged May 20, 1954. Eight days after discharge she was re-admitted because of chills, fever of 103° F. and epistaxis. Cellulitis of the leg was again present and responded to antibiotics. In addition to the antibiotics the patient again received digitalis, vitamins, and a high protein, high carbohydrate, moderate fat diet, and was discharged on June 14, 1954. Because of persisting leg edema she was re-admitted for the

fourth time, one and one-half weeks after discharge. At this time, in addition to her leg edema, she complained of dyspnea and abdominal pain. She received 500 c.c. of blood, digitalis, Mercuhydrin and Diamox. Jaundice, present on admission, became increasingly worse. On July 7 the patient was lethargic and somnolent and had marked epistaxis. The evening of this same day she was moaning, incontinent and semicomatose, with coarse tremors of both upper extremities; she was also hyperreflexic. On July 8 her condition was unchanged except for the suggestion of fetor hepaticus. She was considered to be in hepatic coma, and cortisone was started. The initial dose was 100 mg. three times a day. The following day her condition was unchanged, and the dose of cortisone was increased from 100 mg. three times a day to 500 mg. every 12 hours. The following morning the patient awoke, was alert, rational, coherent and able to take care of her needs. The cortisone was then reduced to 150 mg. every six hours. On July 11, 1954, she was still remarkably improved and the amount of cortisone was reduced to 100 mg. three times a day. On July 13 it was further reduced, to 50 mg. twice a day. The patient continued to be alert and lively, and was up and about. She did well for several days and then left the hospital without permission. On August 25, 1954, three weeks after leaving the hospital, she was re-admitted for her fifth and last time with complaints of pain and swelling of her legs, confusion and stupor for two days. Physical examination revealed a temperature of 103° F.; pulse, 84; irregular respiration, 32; blood pressure, 125/60 mm. of Hg. She was moaning and was semicomatose. There were coarse tremors of both arms, the skin was deeply icteric, and there were spider angiomata over her chest. She had 4 plus pitting edema of

CASE 2

Date	FBS	BUN	Na	K	Cl	CO_2
11-13-51	117	9				
5-27-53	124	15				48
6-2-53			148	3.0	111	
6-8-53			146	4.0	98	
6-15-53			141	3.2	108	
5-1-54	290	20	133	3.0	95	
7-7-54			134	3.1	94	47
7-9-54			145	2.4	110	40
7-10-54			145	2.9	110	45
7-13-54			130	3.1	97	49
8-26-54	79	27	135	3.2	103	43
8-30-54			131	3.4	101	54
8-31-54			147	3.2	101	54
9-1-54			131	3.8	88	52
9-2-54			136	4.7	110	61
9-3-54			135	4.5	114	
9-4-54			137	2.7	101	62
9-5-54			138	2.0	105	72
9-6-54			137	2.5	92	72
9-8-54			142	2.1	92	
9-9-54			138	2.1	93	
9-13-54			137	5.2	92	
9-16-54			133		101	46
9-20-54			132	5.5	116	
9-23-54		33	135	5.5	106	39
9-27-54			135	4.2	108	31
9-30-54			136	4.4	108	32
10-4-54		41	132		111	38
10-6-54			130	3.9	104	33
10-11-54			137	2.4	108	33
10-14-54			136	3.2	112	36

CASE 2

Date	Chol./Est.	Prothr. Time	A/G	Ceph. Floc.	T.T.	Total Bilirubin	Alk. Phos.
11-15-51	160/125	15	3.3/3.0	1+		10 II	5.3 B.U.
5-27-53		22	2.5/5.8			37 II	
5-28-53	100/50		2.4/6.4	3+		33 II	2.3 B.U.
6-8-53	160/65	19	2.9/5.9	3+		27 II	
5-3-54	133/70	22	1.8/3.9	4+	10.7	4.9	12.0 KAU
6-1-54			2.5/3.8		11.0	5.7	
6-24-54		21			8.4	9.9	
7-8-54			2.0/4.0	4+	5.4	10.0	
7-19-54		19	1.5/4.1		10.0	5.7	
8-31-54	39/10	28					
9-2-54	63/39		1.5/4.7	4+	10.9	5.0	11.6
9-13-54	102/60	23		4+	14.6	9.2	10.0
9-27-54	91/59		1.9/3.6	4+	11.2	4.1	9.8
10-4-54				4+	13.4		
10-11-54	85/62		1.6/3.1	4+	11.4	1.6	10.5

Date	WBC	RBC	Hg.	Ht.	ESR	Seg.	Ly.	Eos.
11-14-51	4.9		7			76	24	
11-15-51	3.4		10	24		84	16	
11-20-51	5.4		11			67	28	4
11-23-51	7.3		9.5			75	23	2
11-26-51	7.7		9.8	28		60	40	
5-27-53	11.1			25		75	23	2
5-3-54	7.0		6.5	20	21	68	32	
5-19-54	4.3		5.5			70	30	
6-1-54				22.5				
6-22-54	10.7		3			72	28	
6-28-54			5.4					
7-3-54	7.6		6			67	33	
7-7-54			7	25	28			
8-26-54	17.4		6.2			70	25	
9-2-54				23				
9-8-54	16.4	3.2	10					
9-13-54				32				
9-17-54	7.8		6.5			67	33	
9-20-54	13.4		6.5	26		70	28	
9-27-54	7.0		7.5			67	33	
9-29-54		2.9	8					
10-4-54	7.4		9	31		64	36	
10-11-54				28				
10-13-54	19.2		7.5			70	30	

both lower extremities. Ascites was present. The patient was given digitalis, Mercuhydrin, vitamins and antibiotics. In addition, she received 250 mg. of cortisone every six hours. On August 26, 1954, the patient was more alert and coherent. Improvement progressively increased so that on August 30 she was again rational, alert and able to take nourishment by mouth. The cortisone was reduced to 250 mg. twice a day, and then once a day until September 1, at which time it was stopped. The patient did fairly well until September 11, 1954, when she relapsed into a semicomatose state. She was given cortisone, 250 mg. three times a day for five days and then, because of improvement, the dosage was reduced to 250 mg. twice a day on September 17 and once a day on September 18. During this trial of cortisone, however, congestive failure and ascites became much more severe. She died on September 18, 1954, in pulmonary edema.

Case 3. A 51 year old white female was admitted on July 6, 1954, with the chief complaint of gradually deepening jaundice over a three month period. Since November, 1953, the patient had lost 60 pounds. For the last 20 years the patient had consumed three to four quarts of beer daily, plus whiskey on occasion. During this period her diet was inadequate. Examination on admission revealed the following: temperature, 98.6° F.; pulse, 84; respiration, 20; blood pressure, 130/80 mm. of Hg. There was axillary hair. Spider angiomata were present on the chest and shoulders. The skin and sclerae were icteric. The liver was palpable five fingerbreadths below the costal margin, the spleen two fingerbreadths below the costal margin. The veins of the abdominal wall were distended and prominent. One plus sacral edema was present. A day after admission the patient felt well. She continued to do well until one week after admission, when she became anorexic and lethargic. This progressed to confusion and disorientation on July 21, 1954. She ceased eating completely, and intravenous fluids were required. On July 26, 500 c.c. of blood were given because of anemia. Cortisone, 50 mg. three times a day, was started on July 26 and was increased to 250 mg. every six hours on July 28, when the patient became obtunded. Twenty-four hours later the patient was much improved. She was alert, coöperative and able to take nourishment by mouth. The cortisone was reduced to 250 mg. twice a day and the following day she was more alert, so that the cortisone was reduced to 250 mg. daily and was finally stopped on July 31, 1954. She continued to do well for the next week in spite of a urinary tract infection. On August 5 rectal bleeding was noted, and she became semicomatose. Cortisone was re-instituted; the dosage

CASE 3

Date	BUN	Creat.	FBS	Na	K	Cl	CO_2
7-8	24		88				
7-26	72	2.8					
7-28				132	3.3	98	36
7-29				127	2.0	95	31
7-30				126	2.2	98	40
7-31				132	1.9	99	49
8-6				130	2.6	87	47
8-7				126	3.1	80	45

Date	Prothr. Time	Chol./Est.	A/G	Alk. Phos.	Ceph. Floc.	T.T.	Total Bilirubin
7-18	22		1.9/2.9		4+	28.4	4.1
7-15		106/24	2.0/2.8	19.5	4+	32.8	3.8
		96/21	2.0/2.9	13.7	4+	38.8	4.4
7-28			2.3/2.7		4+	36.5	2.2
8-5		108/38	2.3/2.4	18.6	4+	43.2	1.4

Serology, negative; urinary findings: 7–10 WBC per high power field; sp. gr., 1.012 and 1 and sugar.

Date	WBC	Hg.	Ht.	Seg.	Ly.	Eos.
7-12	10.0	6.8		61	36	2
7-16		8.0				
		4.0				
7-26	7.9	6.9	22	65	35	
7-30		8.5				
8-5		8.5				

consisted of 250 mg. every six hours. The dosage was continued but without improvement in the patient's status. She died on August 7, 1954.

After review of her case it was felt that the urinary tract infection probably tipped the balance in an unfavorable direction and resulted in the terminal hepatic coma. We believe that the patient did not respond because of her marked electrolytic imbalance and rectal bleeding which, in addition to her urinary tract infection, put too much of a load on an already severely damaged liver.

Case 4. A 39 year old white female was admitted on September 16, 1952, to Queens General Hospital. She complained of amenorrhea for six months. The history revealed that the patient had been a heavy drinker for 10 years, consuming 1 to 2 quarts of beer a day. A year prior to admission she had started to drink wine, 1 to 2 quarts a day, with practically no food intake in that period. She noticed progressive enlargement of her abdomen. Examination at that time revealed the following: temperature, 98.6° F.; pulse, 80; respiration, 20; blood pressure, 110/72 mm. of Hg. There were many spider angiomata on the head, chest and shoulders, associated with ecchymotic areas. The liver was seven fingerbreadths below the costal margin to the level of the umbilicus; it was smooth and firm and had a sharp edge. The spleen was palpable two fingerbreadths below the left costal margin. A liver biopsy performed on October 17 showed cirrhosis. She was treated with diet and vitamins and discharged on September 24, 1952. She was admitted for the second time on November 20, 1952, with a two-day history of swelling, redness and pain in the left foot and left great toe. The patient received antibiotics and was discharged November 26, 1952. She was admitted for the third time on June 21,

CASE 4

Date	FBS	BUN	Na	K	Cl	CO_2
9-18-52	92	8				
11-24-52	124	9				
6-24-54	89	12	143	4.2	108	50
6-30-54		18				
7-2-54			137	3.8	96	52
8-9-54		10				
10-4-54			135	6.7	87	70
10-5-54		33	139	2.4	90	66
10-6-54			140	2.2	97	67
10-7-54			139	2.4	97	54
10-8-54			149	2.8	110	48
10-9-54		49	148	3.3	107	58

Date	Chol./Est.	Prothr. Time	A/G	Ceph.	T.T.	Total Bilirubin	Alk. Phos.
9-18-52	265/165	76	4.9/2.0	2+	12.4		6.7
6-24-54	282/161	23 sec	3.2/3.6	4+	15.2	2.4	8.9
7-1-54	225/125	19	2.0/3.3	4+	15.4		
7-6-54			2.9/3.3	4+	11.4	4.6	
7-19-54		24	2.4/3.0		17.6		
8-9-54	218/155		2.6/4.0	4+	17.7	4.8	
8-19-54		24	2.5/3.6		21.8	4.8	6.6
9-2-54	220/123	24	2.4/3.6	4+	19.4	7.2	12.2
9-20-54	246/140		2.7/3.8	4+	17.6	7.0	12.0
10-4-54		27		4+		6.6	7.4
10-7-54			2.9/2.7				
10-18-54		24					
10-19-54	222/127		2.8/2.0	4+	15.2	20.0	4.9

VDRL and urines negative.

CASE 4

Date	WBC	Hg.	Ht.	Seg.	Lymph.
9-16-52	6.4	12.3		75—	25
11-21-52	7.5	13.0		64	36
6-22-54	5.0	10.5		68	32
6-26-54			35		
6-27-54			38		
6-28-54			33		
6-29-54			37		
6-30-54			38		
7-1-54			35		
7-8-54	17.2	8		70	30
8-2-54	4.0	9		69	31
8-3-54		8			
8-9-54	8.7	10		65	35
8-18-54		9			
9-20-54	5.8	9	29	63	37
10-4-54		6	20		
10-6-54		7	24		
10-17-54		7.5	20		
10-18-54			19		
10-19-54			25		

1954, with a two-month history of leg edema and ascites producing shortness of breath; dark urine had been noted for two weeks prior to admission, but jaundice was denied. During the interval from November, 1952, to April, 1954, the patient had been well except for occasional epistaxis. Examination on admission: temperature, 98° F.; pulse, 88; respiration, 20; blood pressure, 110/70 mm. of Hg. The patient was icteric. The liver was tender and five fingerbreadths below the costal margin, and was definitely smaller than at the first examination. The spleen was two fingerbreadths below the left costal margin. Ascites was present; there was 4 plus pitting edema to the knees. The patient was started on a regimen of bed-rest, a salt-free diet, Mercuhydrin, Diamox and vitamins, on which she did well until June 26, 1954, when she vomited about 500 c.c. of blood. A Patton tube was passed but the vomiting continued. The patient was given 2,000 c.c. of blood, and cortisone, 250 mg. every eight hours, was started and continued for four days. Bleeding ceased on June 29. The patient was still semicomatose. On July 1 her condition improved. She became oriented and fully conscious, and her appetite improved. On July 2 the Patton tube was removed. X-ray revealed esophageal varices, and the patient was still passing tarry stools. Ascites recurred on July 15, and on July 23 a paracentesis was necessary, with removal of 4,000 c.c. of amber fluid. On July 30 the patient vomited 1,500 c.c. of blood and was transfused with 2,000 c.c. of blood. For the next several weeks the patient received transfusions, and another paracentesis was necessary. Although the icterus persisted, the edema cleared and the patient was discharged on September 5, 1954. She was admitted for the fourth and last time on September 16, 1954, because of the recurrence of ascites and leg edema. On October 1 she vomited about 1,000 c.c. of blood and received a transfusion. On October 3 she became stuporous, restless and disoriented. A tremor was noted. On October 4 she lapsed into coma. On the same day she received 500 mg. of cortisone, following which she awoke in the evening and took some fluid by mouth. On October 5 she was able to eat, and received 1,000 c.c. of blood and 400 mg. of cortisone. The cortisone was decreased by decrements to 100 mg. and finally stopped on October 8, at which time the patient was out of bed, eating and much improved. Hematemesis recurred on October 10 and October 17. The patient became comatose on October 19 and died on October 20 from exsanguination.

Case 5. A 26 year old female was first admitted to Queens General Hospital on March 26, 1939, for a pain in her lower back. She was discharged soon thereafter with a diagnosis of sacro-iliac sprain. She did well following discharge until 1952, when her abdomen started to swell. She was told by a physician in May, 1952, that she had cirrhosis, and a paracentesis was performed. Following this she received liver injections and Mercuhydrin. Her second admission to Queens General Hospital was on September 8, 1952, for persistent abdominal swelling.

Her history was significant in that she had consumed at least 1 quart of wine a day for about five years and had been on a very poor diet during that period. Her admission examination revealed the following: temperature, 98° F.; pulse, 80; respiration, 24; blood pressure, 100/60 mm. of Hg. She had many spider angiomata on her face. Examination of her heart revealed a presystolic murmur at the apex. The abdomen was distended. No masses were noted. A paracentesis was performed on September 19, 1952, and again on September 23, 1952, following which the patient was discharged. She was re-admitted October 16, 1952, because of a recurrence of the ascites and icterus. A paracentesis was performed on October 18 and 10,000 c.c. of fluid were removed. The patient was then given Mercuhydrin, a low salt diet and vitamins. She was discharged, but was re-admitted for paracentesis on October 31, November 10, November 24, December 8, December 22, 1952, and January 9, 1953; between 5,200 and 9,500 c.c. of fluid were removed on these occasions. Following the last paracentesis, in January, 1953, the patient did fairly well until January, 1954, when the fluid re-accumulated and two paracenteses were done. Following this she did well until March 8, 1954, when a paracentesis yielded 16,000 c.c. of fluid. On March 11, 1954, she was admitted in coma, with no

CASE 5

Date	BUN	FBS	Na	K	Cl	CO_2
9-11-52	11	136				
10-20-52	7	107				
1-4-54	13	68				
3-13-54			146	6.4	96	52
3-15-54	51	105	147	5.0	111	32
3-16-54			141	4.7	106	44
3-17-54			137	5.1	103	
3-18-54			138	4.5		34
3-19-54			133	4.2	105	44
3-20-54			135	4.1	109	25
3-22-54	63		137	4.1	114	
3-23-54			139	4.5	112	22
3-24-54	100		148	4.7	115	23
3-25-54	88			4.6		28
3-26-54	65		152	4.6	116	28
3-29-54	85		148	5.8	120	23
3-30-54			148	5.3	116	27
3-31-54	91		151	5.8	122	28

Date	Prothr. Time	Chol./Est.	A/G	Ceph. Floc.	T.T.	Total Bilirubin	Alk. Phos.
9-11-52		195/105	3.1/4.1			26 II	7.9 B.U.
10-20-52			3.1/2.0	3+		20 II	10.3 B.U.
1-7-54	17	150/110	3.1/3.0	2+			23.8 KAU
3-15-54	17	128/94	2.6/2.6	4+	4.3	2.4	29.2 KAU
3-18-54		167/119	2.6/3.4	4+	2.5	2.6	25.8 KAU

Serology, negative. Urine: no WBC in 1953 and 1954, with 2+ albumin on 3-12-54 and 3-30-54; sp. gr., 1.017; stools, 3-29-54, 4+ positive for blood.

CASE 5

Date	RBC	Hg.	Ht.	WBC	Seg.	Ly.
6-9-53	3.9	12				
1-7-54		9.8		6.1	63	37
3-12-54		8		27.2	85	15
3-15-54				26.8		
3-24-54			42			
3-31-54			36			

history available from the family. Examination at that time revealed a comatose female; pulse, 120; respiration, 24; blood pressure, 110/80 mm. of Hg. There was marked ascites. A paracentesis was done and 6,000 c.c. of amber fluid were removed. On March 12 she was started on cortisone, 250 mg. every six hours. She remained comatose on March 13; on March 14 she was greatly improved and only slightly irrational. On March 15 the cortisone was reduced to 500 mg. a day, and the patient was even more alert. On March 17 the cortisone was reduced to 100 mg. every six hours. On March 18 it was noted that the patient was somewhat more lethargic but was still eating. Cortisone was continued, 100 mg. three times a day, until March 24. On March 26 the patient became semicomatose but responded to blood transfusion. She died suddenly on March 31, 1954.

Case 6. A 38 year old white female was admitted to Queens General Hospital on March 8, 1954. At the time of admission she was irrational and confused. The history was unobtainable from the patient. The family knew little regarding the patient other than that she had been alcoholic for the last two years. Examination on admission revealed the following: temperature, 98° F.; pulse, 88; respiration, 20; blood pressure, 100/50 mm. of Hg. The patient was icteric, and spidery angiomata were noticed over the shoulders and back. The abdomen was distended and tense. A fluid wave and shifting dullness were present. There was 4 plus pitting edema of the legs. A paracentesis, done on admission, yielded 10,000 c.c. of fluid. She was started on Mercuhydrin, vitamins, parenteral fluids and paraldehyde. On March 10, 1954, she lapsed into a coma. The catheterized specimens of urine on March 12 revealed many pus cells, and because of this the patient was given Terramycin intramuscularly. Although she was started on cortisone, 250 mg. every six hours, she died shortly after receiving the second dose.

CASE 6

Date	Na	K	Cl	CO_2	P.T.	Hg.	BUN
3-8	136	3.3	86	63			
3-9					19	8	
3-11	127	3.5	89		20		42
3-12	137		94	39			

Serology, negative.
3-11: chol./est., 120/71; A/G 2.2/2.0; ceph. floc., 3+; T.T., 6.6; alk. phos., 14.2 KAU: total bilirubin, 6.6.

DISCUSSION

The exact nature of hepatic coma still remains obscure. In reported studies there have been no distinctive changes in clinical findings (other than the level of consciousness) or in usual laboratory tests to distinguish it

from other stages of severe liver disease. It has been noted that there is an increase in the concentration of free amino acids in the blood and urine of those in hepatic coma, and that this increase is proportional to the severity of the coma. In addition, high levels of ammonia, phenol, and lactic and pyruvic acids have been found in patients in hepatic coma. However, in spite of these findings, the long continued search for a metabolic toxin in hepatic coma has not been rewarded. In all probability the above changes reflect a fundamental disturbance in the enzyme systems.[11]

The exact mode of action of the steroids in liver diseases and hepatic coma is not known. Schwartz [12] has shown that in massive liver necrosis induced in rats there was an increased survival time in those rats given cortisone. Vorhaus [13] studied the effect of various drugs in hepatic injury in rats induced by carbon tetrachloride, and found that cortisone afforded the greatest protection. Flink and Williams [14] showed that the steroids reduced the level of serum bile and acids in biliary cirrhosis, and postulated that this was due to the anti-inflammatory action of the hormone, which thus improved the ability of the liver to excrete those substances. Roberts has shown increased regeneration of liver tissue in partially hepatectomized rats when treated with ACTH.[15] Brown and Zoellar have shown an improvement in the histologic picture of portal cirrhosis treated with the steroids. This consisted of a clearing of fat and inflammatory reaction. These studies would indicate that the steroids are helpful in liver disease. However, we do not feel that any of these modes of action influenced the recovery from hepatic coma in the six cases we observed. In all these cases the improvement was dramatic and usually came within 24 hours. Certainly none of the effects of steroids described above could be responsible for this abrupt reversal of hepatic coma, as the interval was much too short. One might postulate that the high dosage of cortisone given to the patients treated in this series was capable of reversing some metabolic disturbance responsible for hepatic coma.

The reasons for selecting the dosage schedule as outlined were purely empiric. After reviewing the literature we felt that on the conventional dosage schedules results have not been good, and that the higher dose was therefore indicated. In addition, we felt that by giving larger doses over a short period of time the deleterious side-effects of cortisone, such as increased salt and water retention, glycosuria and psychic disturbances, would be avoided. This was borne out by the results, as none of the cases evidenced these side-effects. Their recovery from coma was prompt and spectacular. It is our belief that a continued trial of high doses of cortisone in cases of hepatic coma is indicated.

Summary

The results in six cases of hepatic coma of high dosage of cortisone are described. With the exception of one case inadequately treated all patients came out of coma dramatically and quickly. In two instances relapses into

coma responded promptly to the same therapy. All six patients showed evidence of advanced hepatic damage and all eventually died of various complications of cirrhosis including coma.

It is felt that a continued trial of high doses of cortisone in hepatic coma is warranted.

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SUMMARIO IN INTERLINGUA

Coma hepatic occurre frequentemente como phenomeno terminal in avantiate cirrhosis atrophic o postnecrotic. In patientes con pre-existente compromissos hepatic, coma pote esser precipitate per agentes hepatotoxic, infection, excessos de activitate physic, uso injudiciose de sedativos o narcoticos, dieta inadequate, hemorrhagia, trauma, o operation chirurgic.

Coma hepatic es associate con un altissime mortalitate. Es presentate un revista de series de casos in que le mortalitate excedeva 90%. A causa de iste alte mortalitate, numerose planos therapeutic ha essite essayate. A parte le usual mesuras supportative—i.e. per exemplo mantenentia del balancia de fluido e electrolytos, correction de anemia, subjection de infectiones, e administrationes de antibioticos, de glucosa intravenose, e de vitaminas—multe drogas ha essite essayate in le effortio de meliorar le multo adverse prognose que es associate con coma hepatic. Le steroides ha essite essayate extensemente in le tractamento de morbo hepatic. Le resultatos usque al presente ha essite controverse. Tamen, nulle del reportos usque nunc publicate mentiona le uso de doses massive del steroides. In nostre serie, sex patientes recipeva 250 mg de cortisona omne sex horas. In plus, illes recipeva le usual therapia supportative e chloruro de kalium. Esseva notate que intra 24 horas, post trovar se initialmente in un stato de coma profunde, iste patientes recomenciava responder e redeveniva alerte, coherente, e capace a acceptar alimentos.

Iste resultatos forma un contrasto acute con le curso natural de patientes in coma hepatic. Usualmente tal patientes remane comatose durante plure dies usque al tempore de lor morte.

Omne le patientes del presente serie moriva subsequentemente ab complicationes del avantiate cirrhosis o in un recurrentia del coma. Tamen—con le exception de un patiente qui moriva intra octo horas post le initiation del therapia—omnes monstrava un prompte e a vices dramatic responsa al therapia per doses massive de steroide.

Nos opina que essayos futur de alte doses de cortisona in casos de coma hepatic es indicate.

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THE MECHANICS OF BREATHING IN NORMAL SUBJECTS AND IN PATIENTS WITH CARDIO-PULMONARY DISEASE *

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A number of reports have appeared during recent years on the changes of the physical properties of the lung in cardiopulmonary diseases.[1-26] Valuable new information has been obtained on the fundamental nature of different disorders, though only a comparatively small number of subjects have been studied. It is the purpose of this report to describe the results on a series of 100 subjects: 25 normal subjects and 75 patients with various types of cardiopulmonary disease.

Material and Methods

The subjects were studied in the basal state and in the supine position. Transpulmonary pressures, instantaneous air flow rates and tidal volumes were continuously recorded. Pulmonary compliance and mean mechanical resistance during inspiration and expiration were determined during quiet breathing and voluntary hyperventilation, using the esophageal balloon technic previously described.[27] Compliance can be defined as volume change per unit pressure change (L./cm.H_2O), and describes the elastic properties of the lung. Mechanical resistance expresses the relation between air flow and flow resistive pressures, and is expressed as cm. H_2O/L./sec. Because of variations in individual breaths, the mean compliance for a series of 10 cycles was taken, and the values were accepted only if they checked within previously described limits with a second series of 10 cycles.[27] Mean mechanical resistance was measured for 2 or 3 cycles and the mean values of these were taken. It was calculated by dividing resistive pressures by instantaneous air flow rates at time intervals of 1/10 or 1/25 of a second, and the means were established by graphical integration of the individual values for both the inspiratory and the expiratory phases of the respiratory cycle. Vital capacity and maximal breathing capacity were measured the same day. The prediction formulae of Baldwin [28] were used for the calculation of the air velocity index. Whenever necessary, lung volume determinations, intrapulmonary mixing and analysis of arterial blood gases were carried out to

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establish a functional diagnosis. In addition, the cardiac patients underwent right heart or combined heart catheterization.*

Normal Subjects: The normal group is characterized by a compliance which is independent of respiratory rate as long as the respiratory midposition is constant. In fact, this is one of the criteria we use at present for the definition of a normal ventilatory function. There is no significant difference between inspiratory and expiratory mechanical resistance.

TABLE 1

Classification of Patients

Group of Patients Studied	Total No. of Subjects Studied	No. of Subjects Studied in Each Subgroup	Reference No. in Tables
Normals	25		1–25
Bronchospastic Disease	38		
Allergic bronchitis		2	77–78
Chronic bronchial asthma		10	52–61
Chronic pulmonary emphysema		26	26–51
without cor pulmonale		(14)	27, 32, 33, 36–38, 40, 42, 47, 49–51
with cor pulmonale		(12)	26, 28–31, 35, 39, 41, 43, 44, 46, 48
Restrictive Pulmonary Disease	10		
Calcified pleura		1	62
Spontaneous pneumothorax		3	63–65
Pleural effusion		3	66–68
Pectus excavatum		1	69
Massive atelectasis		1	70
Postpneumonectomy		1	71
Pulmonary Fibrosis	5		72–76
Cardiovascular Disease	22		
Systemic arterial disease		3	79–81
Large intracardiac shunts (noncyanotic)		4	82–85
Mitral stenosis		15	86–100
without pulmonary hypertension, compensated		(1)	87
with pulmonary hypertension, compensated		(5)	92, 93, 95, 97, 99
with pulmonary hypertension, uncompensated, normal arterial O_2 saturation		(5)	89, 90, 94, 96, 98
with pulmonary hypertension, uncompensated, arterial O_2 unsaturation		(4)	86, 88, 91, 100

The patients were classified into six different groups according to clinical history, x-ray findings, and the above described function studies. When there was a combination of diseases, the patients were grouped according to the predominating pathologic feature. The classification of the patients is summarized in table 1. Several of the patients have been listed repeatedly because they were studied on different occasions.

Results: The results are listed in tables 2 through 8 and illustrated in figures 1, 2 and 3.

* Catheterization studies were carried out by Dr. J. Dow in the Circulation Laboratory at the Boston City Hospital. These patients will be reported in more detail elsewhere.[29]

TABLE 2

The Mechanics of Breathing in 25 Normal Patients in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O/L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Exp. Resistance s,* cm. $H_2O/L./sec.$	Mean Insp. Resistance f,* cm. $H_2O/L./sec.$	Mean Exp. Resistance f,* cm. $H_2O/L./sec.$
1. J. T.	M	23	1.86	4.0	.128	.069	.032	.09	—	—	6.5	6.6	3.6	3.9
2. E. S.	M	23	2.38	6.0	.130	.055	.022	—	—	—	2.85	3.55	—	—
3. B. D.	M	35	1.84	4.3	.136	.074	.032	.116	115	.90	2.70	1.6	1.62	1.72
4. W. C.	M	37	1.7	3.5	.223	.131	.064	.225	—	—	1.30	1.9	—	—
5. J. R.	F	21	1.56	3.2	.105	.067	.033	.082	96	1.0	5.40	7.3	5.0	5.3
6. M. G.	M	30	1.8	4.5	.150	.083	.033	.147	140	1.05	3.00	4.3	3.0	3.0
7. M. G.	M	30	1.8	4.7	.160	.089	.034	.120	184	1.33	2.80	2.80	3.65	4.2
8. C. B.	M	37	1.78	3.6	.107	.060	.030	.085	—	—	3.30	3.40	5.8	5.1
9. M. D.	M	27	1.83	5.2	.195	.107	.037	.21	144	.92	3.00	2.30	2.8	2.9
10. C. R.	M	28	1.91	4.1	.158	.083	.039	.132	138	1.08	3.95	6.25	4.75	5.2
11. S. W.	M	28	1.87	5.1	.152	.081	.029	.178	145	.90	1.88	2.90	2.0	2.15
12. H. P.	M	32	1.9	4.2	.145	.076	.034	.162	151	1.13	4.40	4.60	2.7	3.0
13. B. C.	M	28	1.8	4.0	.228	.127	.057	.224	122	.94	3.45	3.20	3.45	5.15
14. T. E.	M	32	2.16	5.2	.218	.101	.042	.232	151	.87	2.10	2.50	1.3	1.3
15. H. M.	M	23	2.18	6.1	.142	.065	.023	.133	149	.70	2.10	2.40	2.5	2.2
16. M. W.	M	32	2.14	4.3	.157	.073	.036	.121	97	.66	5.50	3.50	1.6	5.5
17. F. C.	M	27	1.86	5.1	.224	.120	.044	.226	124	.79	3.00	3.50	2.2	2.3
18. H. S.	M	29	1.77	5.0	.126	.071	.025	.110	132	.87	1.30	1.90	3.1	1.4
19. C. B.	M	33	1.98	5.0	.147	.074	.039	.142	170	1.0	2.00	3.45	1.5	2.65
20. R. W.	M	31	1.91	5.2	.242	.127	.046	.190	160	.97	1.20	1.30	1.35	2.25
21. H. L.	M	24	1.95	5.4	.187	.096	.035	.149	162	.93	2.20	4.40	1.2	1.3
22. T. S.	M	25	1.91	5.0	.139	.073	.028	.137	134	.85	2.95	3.30	3.25	3.0
23. D. M.	M	27	2.2	6.2	.148	.067	.024	.120	205	.99	1.70	2.50	1.2	1.4
24. I. H.	M	27	2.02	5.2	.188	.093	.036	.170	175	1.02	2.60	2.90	1.6	2.2
25. L. M.	M	29	1.76	4.45	.110	.062	.027	.103	106	.86	2.70	4.45	2.3	2.6
Mean				4.7	.162	.085	.035	.150	143	.94	2.95	3.45	2.67	3.03
Standard Deviation					±.04	±.022	±.01	±0.047			±1.34	±1.51	±1.26	±1.38

* s = slow.
* f = fast.

TABLE 3

The Mechanics of Breathing in 26 Patients with Chronic Pulmonary Emphysema in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O/L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Exp. Resistance s,* cm. $H_2O/L./sec.$	Mean Insp. Resistance f,* cm. $H_2O/L./sec.$	Mean Exp. Resistance f,* cm. $H_2O/L./sec.$
26. H. H.	M	59	1.61	0.9	.043	.027	.048	.019	23	0.99	8.30	26.50	5.50	41.50
27. H. H.	M	59	1.97	2.5	.250	.127	.100	.118	45	0.62	5.70	8.50	3.75	9.20
28. W. H.	M	49	1.99	1.9	.028	.014	.015	.018	—	—	38.80	41.80	29.00	76.00
29. M. A.	M	59	1.70	2.0	.111	.065	.056	—	54	0.92	6.95	7.85	—	—
30. J. S. (1)	M	47	1.60	2.7	.070	.044	.026	.046	—	—	—	—	—	—
(2)	M	47	1.61	2.3	.070	.044	.030	.025	50	0.65	8.00	8.00	8.25	17.80
(3)	M	48	1.63	1.6	.076	.047	.047	.045	32	0.75	7.00	7.00	7.80	15.25
31. P. T.	M	68	1.90	2.8	.400	.210	.143	—	—	—	5.80	12.40	—	—
32. F. M.	M	64	1.61	2.2	.162	.101	.074	.055	22	0.40	6.20	16.50	7.55	23.40
33. M. N. (1)	M	50	1.68	3.0	.124	.074	.041	.078	51	0.63	9.36	13.80	8.75	8.40
(2)	M	50	1.68	2.2	.111	.066	.050	.040	47	0.73	6.60	9.50	5.65	7.75
34. M. P.	M	67	1.72	3.0	.148	.086	.049	.092	49	1.00	6.80	13.40	10.70	15.90
35. M. N. (1)	M	56	1.83	2.4	.166	.091	.069	.111	65	0.92	14.60	29.30	—	—
(2)	M	56	1.83	2.2	.097	.053	.044	.037	—	—	11.70	11.70	—	—
36. N. S.	M	64	1.85	3.0	.072	.039	.024	.064	—	—	9.00	21.20	6.10	8.30
37. W. J.	M	61	2.07	2.7	.132	.064	.044	.094	50	0.48	9.00	9.00	7.20	20.00
38. A. B.	M	61	1.53	3.3	.139	.091	.040	.050	32	0.40	10.20	15.20	8.90	14.50
39. J. S.	M	55	1.77	3.5	.071	.040	.020	.022	61	0.62	10.10	48.00	10.30	27.00
40. A. B.	M	56	1.76	3.4	.097	.055	.028	.071	100	1.12	5.30	9.60	3.50	4.90
41. P. J.	M	58	1.54	1.8	.051	.033	.028	—	12	0.29	12.00	12.30	—	—
42. M. S.	M	48	1.66	4.2	.118	.071	.028	.064	115	0.94	4.20	4.70	3.10	5.60
43. B. J.	M	63	2.04	2.7	.050	.025	.014	.042	54	0.71	14.30	14.50	—	—
44. S. G.	M	52	1.85	1.4	.061	.033	.017	.033	18	0.41	15.60	43.40	—	—
45. W. B.	M	61	1.62	1.9	.159	.036	.016	.035	25	0.55	7.85	25.50	7.55	15.40
46. E. D.	M	49	1.94	4.4	.120	.062	.027	.130	104	0.75	4.10	8.50	4.25	4.05
47. D. P.	F	39	1.64	1.4	.168	.087	.120	.068	93	0.25	2.65	3.70	2.10	2.40
48. A. D.	M	58	1.76	1.8	.349	.198	.194	.052	26	0.50	11.50	22.51	6.00	9.70
49. R. D. (1)	M	63	1.85	2.6	.097	.052	.029	.072	87	1.15	7.80	14.90	5.70	6.10
(2)	M	63	1.85	2.1	.079	.043	.038	.078	75	1.25	15.25	25.90	4.20	6.60
50. E. F.	M	54	1.73	2.2	.088	.051	.040	.033	32	0.54	11.10	24.30	8.60	25.10
51. J. P.	M	49	1.68	2.6	.330	.196	.084	.043	37	0.56	6.00	16.80	4.60	29.40
Mean				2.5	.130	.072	.051	.058	54.3	0.70	9.73	17.54	7.23	16.73
Standard Deviation					±.082	±.050	±.004	±.030			±6.44	±11.42		

* s = slow.
* f = fast.

TABLE 4

The Mechanics of Breathing in 10 Patients with Chronic Bronchial Asthma in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O./L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Resistance s,* cm. $H_2O/L./sec.$	Mean Resistance f,* cm. $H_2O/L./sec.$	Mean Resistance f,* cm. $H_2O/L./sec.$
52. F. W.	M	35	1.82	5.7	.100	.055	.018	.068	—	—	7.25	7.25	6.80	6.90
53. S. S.	M	24	2.03	4.6	.129	.064	.028	.104	—	—	10.40	19.50	—	—
54. B. K.	M	33	2.04	3.6	.104	.051	.029	.086	41	.36	7.00	11.00	6.60	12.30
55. M. F. (1)	F	36	1.61	2.9	.190	.118	.065	.160	65	.77	3.80	8.40	3.80	4.50
(2)	F	36	1.61	2.1	.124	.077	.059	.056	—	—	9.70	11.40	7.25	12.90
(3)	F	36	1.61	0.9	.072	.045	.024	.062	—	—	26.40	25.40	7.50	14.90
56. R. J. (1)	F	34	1.69	2.0	.038	.023	.019	.027	65	1.09	12.80	16.00	9.40	14.80
(2)	F	34	1.69	1.6	.030	.018	.019	—	48	0.97	41.50	61.00	—	—
57. H. P. (1)	M	16	1.85	3.6	.167	.090	.046	.131	114	1.03	3.25	4.25	3.65	3.30
(2)	M	16	1.85	2.5	.089	.048	.036	.048	73	0.9	7.20	9.65	5.70	8.45
(3)	M	16	1.89	3.8	.100	.053	.026	.106	108	0.93	4.45	5.30	3.00	3.95
58. M. G.	F	31	1.84	2.7	.108	.059	.040	.058	43	0.35	10.90	21.80	8.70	12.00
59. E. N.	M	49	1.81	3.0	.090	.050	.030	.105	82	.88	6.95	13.50	3.75	6.55
60. A. S.	M	28	1.92	4.0	.144	.075	.036	.089	85	.70	3.00	4.60	2.50	3.30
61. B. P.	M	44	1.80	2.7	.098	.054	.036	.035	37	.47	24.00	33.80	13.50	61.00
Mean				3.0	.106	.059	.034	.081	69	.77	11.9	16.86	6.32	12.68
Standard Deviation					±0.041	±.025	±0.014	±.038			±10.8	±14.8		

* s = slow.
* f = fast.

TABLE 5

The Mechanics of Breathing in 10 Patients with Restrictive Pulmonary Disease in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O/L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Exp. Resistance s,* cm. $H_2O/L./sec.$	Mean Insp. Resistance f,* cm. $H_2O/L./sec.$	Mean Exp. Resistance f,* cm. $H_2O/L./sec.$
62. W. F.	M	73	1.7	2.8	.146	.086	.052	.080	65	1.04	3.20	6.80	2.40	4.50
63. H. S.	M	32	1.8	1.1	.045	.025	.041	.045	—	—	3.10	4.90	2.80	4.30
64. W. C.	M	49	1.65	3.8	.143	.087	.038	.162	128	1.33	2.20	2.54	2.83	2.80
65. H. T.	M	20	1.65	2.2	.112	.068	.051	.107	80	1.28	1.50	2.50	2.40	3.00
66. C. B.	M	45	1.8	1.5	.046	.026	.031	—	—	—	3.75	5.20	—	—
67. M. A.	M	65	1.53	2.5	.080	.057	.035	.069	47	1.77	4.75	8.80	5.25	5.50
68. G. A.	M	56	1.97	2.7	.105	.053	.039	.084	114	1.38	5.70	10.60	3.10	5.75
69. K. N.	F	15	1.47	2.0	.046	.031	.023	.04	67	1.16	8.40	9.40	6.60	5.60
70. E. J.	M	63	1.72	1.5	.058	.034	.039	.057	52	1.00	6.80	10.70	8.90	9.90
71. B. B.	M	65	1.67	2.2	.045	.027	.020	.028	35	0.57	13.00	13.60	12.50	17.00
Mean				2.2	.083	.049	.037	.075	73.5	1.11	5.24	7.50	5.20	6.48
Standard Deviation					±.041	±.024	±0.01	±.041		1.07	±3.45	±3.72		

* s = slow.
* f = fast.

TABLE 6

The Mechanics of Breathing in Five Patients with Intrapulmonary Fibrosis in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O/L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Exp. Resistance s,* cm. $H_2O/L./sec.$	Mean Insp. Resistance f,* cm. $H_2O/L./sec.$	Mean Exp. Resistance f,* cm. $H_2O/L./sec.$
72. A. D.	F	51	1.56	1.7	.052	.033	.031	.025	—	—	12.20	19.30	6.50	9.80
73. F. P.	M	50	1.94	3.6	.130	.067	.036	.102	127	1.17	3.30	3.20	—	—
74. C. F. (1)	M	47	1.50	3.4	.077	.051	.023	.100	168	1.99	1.10	1.60	0.70	1.00
(2)	M	47	1.56	3.4	.113	.072	.033	.128	148	1.67	1.85	4.75	0.55	2.15
75. M. M.	F	59	1.78	1.0	.025	.014	.025	.011	43	0.77	10.50	24.50	13.9	25.90
76. T. D.	M	56	1.63	1.1	.038	.023	.035	.022	40	1.41	4.40	11.70	5.2	10.60
Mean				2.4	.072	.043	.030	.065	105	1.40	5.56	10.84	5.36	9.88
Standard Deviation					±.042	±.024	±.005	±.051			±4.66	±9.38		

* s = slow.
* f = fast.

TABLE 7

The Mechanics of Breathing in Six Patients with Allergic Bronchitis in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. $M.^2$	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per $M.^2$ B.S., L./cm. $H_2O/m.^2$	Compliance per Liter Vital Capacity, L./cm. $H_2O/L.$	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. $H_2O/L./sec.$	Mean Exp. Resistance s,* cm. $H_2O/L./sec.$	Mean Insp. Resistance f,* cm. $H_2O/L./sec.$	Mean Exp. Resistance f,* cm. $H_2O/L./sec.$
77. B. M.	M	35	1.79	3.8	.097	.054	.026	.046	98	0.95	3.2	4.60	2.20	2.20
78. H. P.	M	32	1.90	4.0	.169	.097	.042	.111	166	1.31	2.6	5.30	3.25	6.50
Mean				3.9	.133	.075	.034	.078	132	1.13	2.9	4.95	2.73	4.35

* s = slow.
* f = fast.

TABLE 8

The Mechanics of Breathing in 23 Patients with Cardiac Vascular Disease in Supine Position During Slow and Fast Respiratory Rates

Name	Sex	Age	B.S. M.²	Vital Capacity, Liters	Compliance, Slow Rate, L./cm. H_2O	Compliance per M.² B.S., L./cm. H_2O/m.²	Compliance per Liter Vital Capacity, L./cm. H_2O/L.	Compliance, Fast Rate, L./cm. H_2O	Max. Breathing Capacity, L./min.	Air Velocity Index	Mean Insp. Resistance s,* cm. H_2O/L./sec.	Mean Exp. Resistance s,* cm. H_2O/L./sec.	Mean Insp. Resistance f,* cm. H_2O/L./sec.	Mean Exp. Resistance f,* cm. H_2O/L./sec.
79. T. B.	M	55	1.77	3.7	.210	.119	.057	.189	84	0.85	0.97	2.14	1.99	2.79
80. E. B.	M	51	1.85	3.0	.089	.048	.030	.068	91	1.00	3.45	5.60	2.80	4.10
81. R. G.	M	23	1.82	3.5	.145	.080	.041	.096	130	1.18	2.35	5.35	2.60	3.60
82. E. C.	F	28	1.57	3.2	.074	.047	.023	.086	61	0.68	4.70	1.65	1.65	3.85
83. J. O.	F	22	1.36	1.2	.064	.047	.053	.034	51	1.56	9.00	7.60	6.60	9.80
84. H. E.	F	15	1.44	2.9	.062	.043	.021	.068	82	0.99	3.60	4.70	2.75	3.40
85. C. B.	F	47	1.58	1.6	.024	.015	.015	.029	60	1.38	13.50	21.30	4.50	7.80
86. J. P.	F	48	1.44	1.5	.056	.039	.037	.038	46	1.10	7.45	10.70	5.75	9.60
87. M. M.	F	23	1.62	2.0	.078	.048	.039	.060	132	2.35	2.50	5.70	2.60	3.10
88. M. H.	F	52	1.49	1.6	.052	.035	.032	.052	73	1.75	3.80	5.05	3.50	6.05
89. E. O.	F	17	1.57	2.2	.058	.037	.026	.050	83	1.31	2.10	5.30	1.90	2.80
90. L. H.	F	26	1.55	1.2	.074	.048	.062	.068	32	0.85	3.90	6.30	1.30	4.45
91. L. F.	M	44	2.04	1.5	.058	.029	.039	.042	66	1.44	4.80	6.80	3.05	3.90
92. T. D.	M	42	1.63	3.2	.107	.066	.033	.089	74	0.86	6.10	9.30	6.00	7.20
93. S. P.	M	31	1.95	3.3	.086	.044	.026	.094	108	1.08	6.10	10.50	4.10	7.15
94. L. M.	M	45	1.60	2.6	.102	.064	.039	.090	73	0.99	3.60	7.25	3.50	5.50
95. J. Q.	M	23	1.76	4.7	.074	.042	.016	.070	132	0.93	6.70	9.00	3.70	4.25
96. D. S.	F	39	1.53	2.4	.053	.035	.022	.041	68	1.00	4.90	4.70	2.60	6.60
97. A. C.	F	22	1.47	2.6	.066	.045	.025	.059	95	1.21	5.10	6.10	3.00	4.60
98. R. M.	F	42	1.61	2.0	.086	.053	.043	.064	51	0.89	3.95	7.75	2.15	2.20
99. T. E. (1)	M	47	1.58	2.1	.150	.095	.071	.067	55	0.95	3.40	5.15	4.60	6.85
(2)	M	47	1.58	1.8	.136	.086	.075	.067	61	0.79	4.30	7.80	5.60	6.90
100. S. H.	M	39	1.65	2.3	.168	.102	.073	.084	52	0.78	6.65	15.60	5.20	10.60
Mean				2.4	.090	.055	.039	.070	77	1.13	4.91	7.45	3.54	5.53
Standard Deviation					±.043	±.025	±.018	±.032			±2.45	±4.46		

* s = slow.
* f = fast.

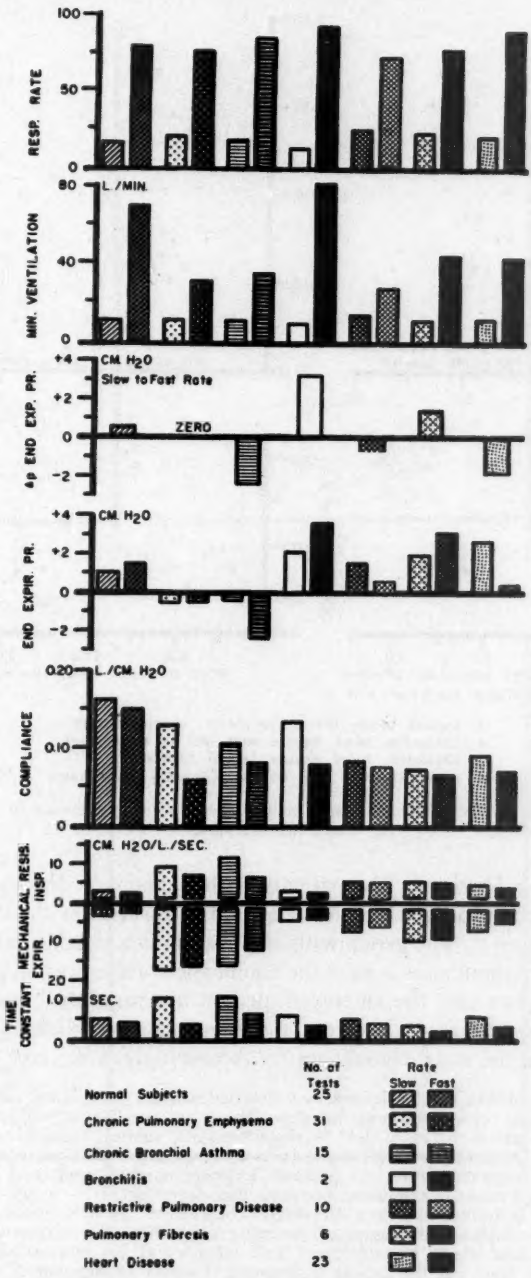

FIG. 1. Mechanics of breathing (mean values) in 25 normal subjects and in 75 patients (87 measurements) with cardiopulmonary disease.

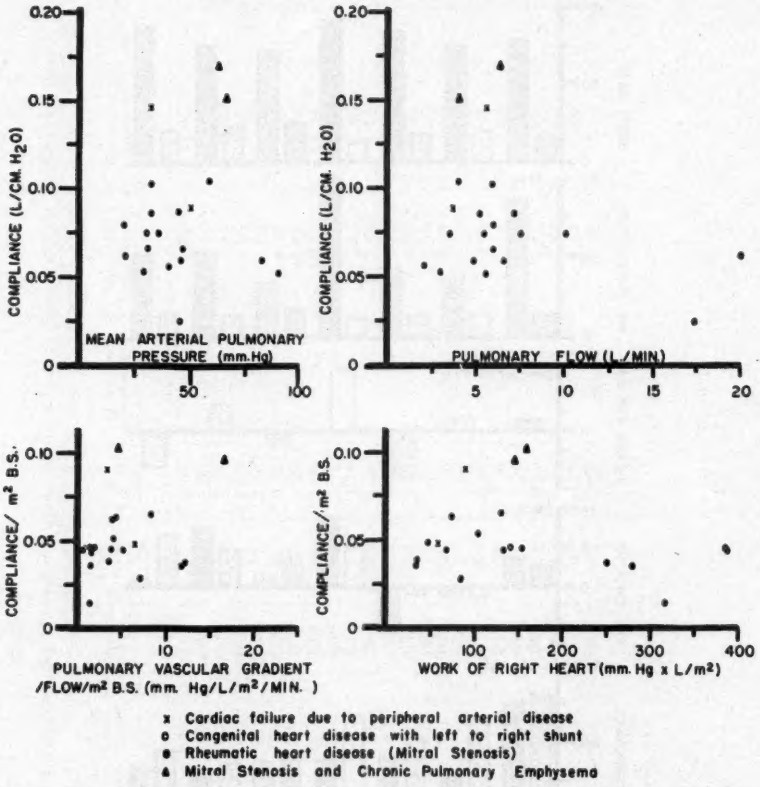

FIG. 2. Relation between compliance and pulmonary hemodynamics in 22 patients with heart disease.

Pulmonary Diseases: The patients with pulmonary disease are characterized by a compliance which is considerably lower than the compliance of the normal group. The group with emphysema is a notable exception, inasmuch as their compliance is near the compliance of the normal group. This is due to the fact that the employed method measures the "functional compliance." In emphysema patients the functional compliance can be quite different from the static compliance.* Accordingly, voluntary hyperventila-

* Static compliance can be defined as a flow-independent compliance. If distribution of ventilation changes with respiratory rate, compliance and mechanical resistance decrease as the respiratory rate is increased.[12, 30, 31] In the normal subject, compliance is independent of frequency of respiration; therefore, it is assumed that the distribution of ventilation is independent of respiratory rate. In patients in whom unequal ventilation is present, particularly in emphysema, compliance becomes flow-dependent,[12, 14, 32] i.e., an increase in respiratory rate is associated with a decrease in compliance. In these patients, the measurement of static compliance is hampered by many difficulties. To measure the true static compliance, air flow has to be interrupted until intrapleural (or intra-esophageal) pressure reaches a steady level. If the patient is dyspneic, this may be impossible. The compliance

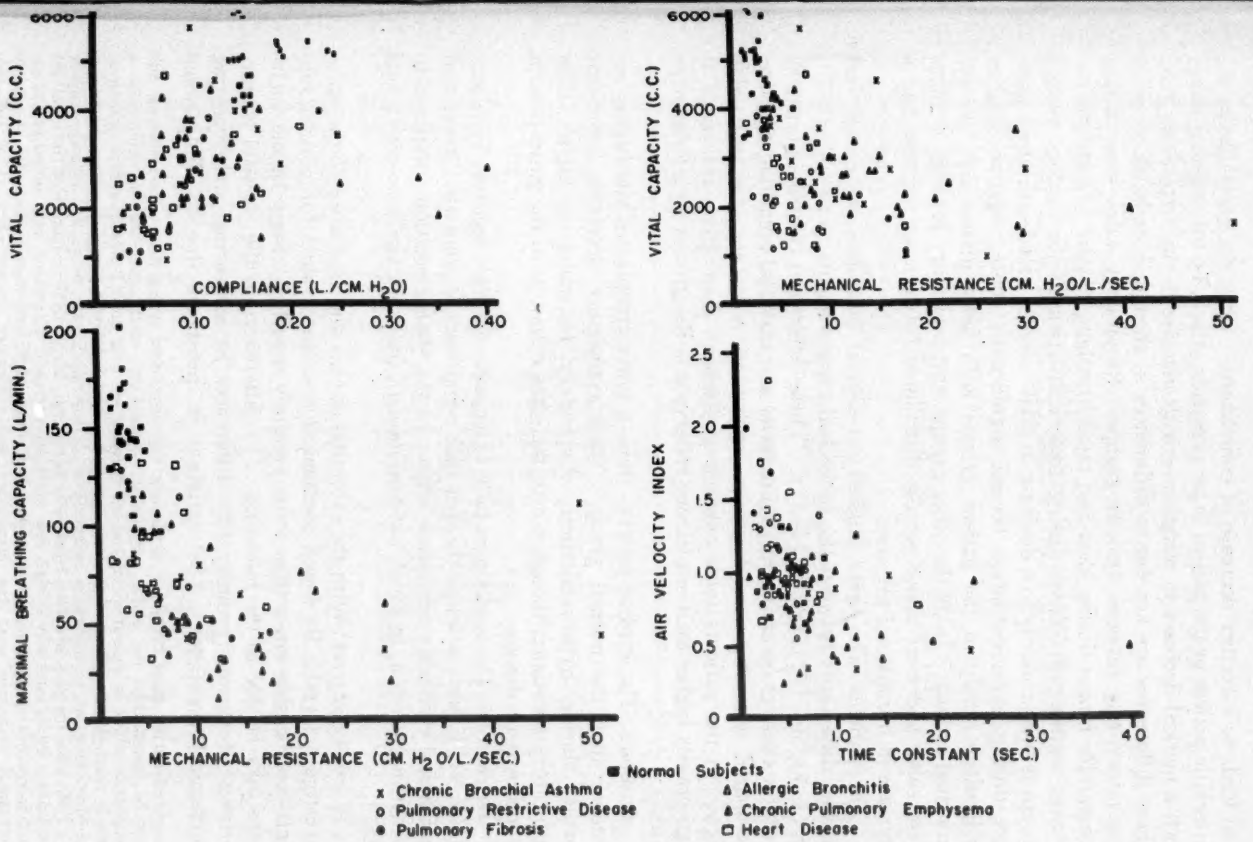

FIG. 3. Compliance and mechanical resistance in relation to vital capacity, maximal breathing capacity and air velocity index in 25 normal subjects and 75 patients (87 measurements) with cardiopulmonary disease.

tion leads to a further decrease of compliance. With the exception of the bronchitic patient or the patient in an asthmatic attack, no other group shows such a marked decrease in compliance with increase in the respiratory rate. These differences are not due to differences in change in midposition or of respiratory rate between various groups. Respiratory rates were within comparable ranges during slow and rapid breathing (figure 1), and the decreased ventilatory volume during hyperventilation in the various patient groups is due primarily to a decrease in tidal volume. End-expiratory pressure during hyperventilation became significantly more negative (higher midposition) only in the patient groups with heart disease and chronic bronchial asthma. In all the other groups, end-expiratory pressure changes were small and were about equally distributed between an increase and a decrease in intrapleural pressure.

The patients who were studied on several occasions sometimes had marked differences between the individual measurements (cases 49 (1–2), 55 (1–3), 56 (1–2), and 57 (1–3)). These differences correlate quite well with the changes occurring in vital capacity and maximal breathing capacity. Compared with the normal group, mechanical resistance is considerably higher in the patients with pulmonary disease. Expiratory resistance is significantly higher than inspiratory resistance in the groups with pulmonary disease.

Cardiacs: The cardiac patients show a lower compliance and higher resistance than the normal group. Their compliance decreases somewhat further during hyperventilation. Expiratory resistance is higher than inspiratory resistance, though not to the same extent as in the patients with bronchospastic disease.

Discussion: The values generally agree with the ones reported by others (table 9), if one considers the fact that compliance is somewhat lower and mechanical resistance somewhat higher in the supine position compared to the sitting position, in which position most of the other studies were carried out.

Normal Subjects: With the exception of Otis and Bembower,[22] the other investigators (table 9) found mechanical resistance values for normal subjects considerably lower than those presently reported. Some of the variations may be due to the following: (1) differences in the physical characteristics of various groups; (2) differences in measuring and reporting mechanical resistance,* (3) variation in resistance due to dimensional

measured during quiet breathing is already flow-dependent under these circumstances, and may be lower than the static compliance. Functional compliance can be defined as a compliance which is measured without interrupting air flow until a steady intrapleural pressure is reached. It follows that static compliance and functional compliance are identical if the distribution of ventilation is independent of respiratory rate, as in the normal subjects.

* Because the pressure-flow relation is not linear, mechanical resistance varies over the respiratory cycle, especially if high flow rates are present. Therefore, most investigators report mechanical resistance for a given flow rate, while our results describe the mean mechanical resistance over the inspiratory and expiratory phases. Fry et al. separate mechanical resistance into its laminar and turbulent components, and report the coefficients for both.[10]

TABLE 9

Compliance and Mechanical Resistance in Normal Subjects and in Patients with Cardiopulmonary Disease: Results of Different Investigators

Reference	No. of Subjects Studied	Diagnosis	Static Compliance, L./cm. H_2O	Functional Compliance, L./cm. H_2O	Compliance During Hyperventilation, L./cm. H_2O	Insp. Mech.¶ Resistance, cm. H_2O/L./sec.	Exp. Mech.¶ Resistance, cm. H_2O/L./sec.
Otis et al.[22, 22**]	20	Normal	.210§	—	—	2.80	—
*Frank et al.[4]	70	Normal	.165	.194‖	—	—	—
*Cherniak[12]	7	Normal	.201	.197	—	1.71ˣ	—
						0.23ˣˣ	
*Marshall and Du Bois[24]	12	Normal	—	.170	—	1.20	—
*Du Bois et al.[3]	21	Normal	—	—	—	1.50ˣˣˣ	—
*Fry et al.[9,10]	12	Normal	.023	—	—	1.50ˣ	—
						0.71ˣˣ	
*Mead et al.[12]	10	Normal	—	.225	—	1.90	1.90
*McIlroy et al.[2]	10	Normal	—	.131	.224°°°	—	—
†This paper	25	Normal	—	.162	.150	2.95	3.45
*Cherniak[12]	12	Chronic pulmonary emphysema	.397	.198	—	3.76ˣ	—
						1.02ˣˣ	
*Fry et al.[9,10]	10	Chronic pulmonary emphysema	—	.180	—	6.04ˣ	—
						1.87ˣˣ	
*Mead et al.[12]	10	Chronic pulmonary emphysema	.500	.170	.040	11.70	24.70
*Marshall and Du Bois[26]	7	Chronic pulmonary emphysema	—	.221	—	3.49	—
†This paper	14	Chronic pulmonary emphysema	—	.142	.066	7.69	15.50
*Cherniak[12]	6	Chronic pulmonary emphysema; cor pulmonale	.140	.050	—	6.11ˣ	—
						2.88ˣˣ	
†This paper	12	Chronic pulmonary emphysema; cor pulmonale	—	.117	.048	12.05	20.98
†Marshall and Christie[7]	7	Pneumonia	—	.056	—	2.33ˣ	—
						1.05	
*Marshall and Du Bois[26]	5	Kyphoscoliosis	—	.064	—	3.35	—
†This paper	10	Restrictive lung disease	—	.083	.075	5.24	7.50
*Marshall and Du Bois[26]	19	Pulmonary fibrosis	—	.098	—	2.23	—
†This paper	5	Pulmonary fibrosis	—	.072	.065	5.56	10.84
*McIlroy and Marshall[17]	9	Asthma	—	.055	.033°°°	14.40	—
*Marshall and Du Bois[26]	7	Asthma	—	.094	—	4.61	—
†This paper	10	Asthma	—	.106	.081	11.90	16.86
‡Scherrer et al.[25]	8	Asthma°	—	.130	—	5.75	9.80
‡Scherrer et al.[25]	8	Asthma°°	—	.038	—	27.25	40.00
‡Marshall et al.[16]	25	Mitral stenosis	—	.092	—	—	—
*Hayward and Knott[29]	30	Mitral stenosis	—	.083	.056°°°	—	—
*Brown et al.[19]	17	Heart disease	—	.119	—	2.63ˣ	—
						1.02ˣˣ	
*Marshall and Du Bois[26]	6	Heart disease	—	.089	—	2.23	—
†This paper	22	Cardiovascular disease	—	.090	.070	4.91	7.45

* Sitting up.
† Supine position.
‡ Position not stated.
§ 8 subjects.
‖ 18 subjects.
¶ Values can be compared only if differences in measuring methods are considered.
° During asthma-free interval.
°° During induced asthmatic attack.
°°° During exercise.
ˣ Coefficient of linear resistance.
ˣˣ Coefficient of turbulent resistance.
ˣˣˣ During panting, airway resistance only.

changes of the upper airways (cheeks, tongue and glottis);[1, 3] (4) different body positions.[27, 32] In addition, it has been shown that mechanical resistance varies to a great extent with changes in the respiratory midposition.[1, 10, 33] Butler and Arnott [33] demonstrated that breathing at a midposition just below 30% of the vital capacity increases the viscous work about four times. This increase is due to an increase in mechanical resistance, whereas the changes in elastic work occurring with changes in midposition are due primarily to the different pressures necessary to keep the lung inflated at a given midposition, rather than to changes in compliance. This finding, and the nonlinear pressure-flow relationship, may account for the wide range of mechanical resistance in normal subjects, in contrast to the rather uniform results in compliance measurements.

Pulmonary Diseases: The herein reported results allow to some extent a differentiation of various pulmonary diseases. *Bronchospastic disease* (i.e., chronic bronchitis, bronchial asthma and pulmonary emphysema) is characterized by increased mechanical resistance. The increase of expiratory resistance is often out of proportion to the increase in inspiratory resistance (see cases 26, 31, 32, 34, 35, 36, 38, 39, 44, 45, 46, 48, 49, 50, 51, 53, 58, 59, 61, 75 and 85). This may be due in part to ball-valving. The latter factor also accounts for considerable variation in expiratory resistance between individual breaths, and is especially prominent during high expiratory flow rates. Because bronchospastic disease is associated with unequal ventilation, the functional compliance may be low, and may drop markedly during hyperventilation. At the same time, a drop in mechanical resistance occurs during hyperventilation if ball-valving does not interfere to a great extent. During a remission, patients with chronic bronchial asthma may show values for compliance and resistance within the normal range (see cases 55, 57 and 60).

There is, however, a basic difference between the patients with chronic pulmonary emphysema and those with other bronchospastic diseases. Due to marked disturbance of visco-elastic properties in the emphysematous lung, these patients usually have a high static compliance. As a result, the correlation between vital capacity and compliance, which is quite good in all the other groups, is poor in patients with chronic pulmonary emphysema, and the values of compliance per liter of vital capacity are significantly higher than are those in all other groups (tables 2–8).

The changes in the elastic properties in emphysema are, in a few patients (cases 27, 30, 37, 40, 42, 46 and 47), associated with a relatively small increase in resistance. One wonders if their basic pathology differs from that observed in the classic type of chronic obstructive emphysema. The latter is usually characterized by marked increase in mechanical resistance, especially during expiration, whereas the pathology in the first group is confined mainly to elastic changes.

It is of interest to compare the results in patients with and those without cor pulmonale. Table 9 shows that, in general, the compliance of the

emphysema patients with cor pulmonale is lower and the resistance higher than they are in the patients without cor pulmonale. In Cherniak's patients,[13] this difference is much more striking than in the present study. Cases 31 and 48 showed the highest functional compliance in the emphysema group, though they were in cardiac failure at the time of study. Because the emphysematous lung is characterized by a marked decrease of elastic retractability, due to the diminished number of alveolar membranes, it seems likely that the elastic properties of the emphysematous lung are particularly influenced by changes in the intrapulmonary blood volume. However, the measured compliance is the result of a number of different factors (physical characteristics of the lung and the vasculature, blood flow, and ventilation), the interrelation of which is not clearly understood.

The employed method does not allow a differentiation between the resistance to air flow and the resistance to tissue deformation. However, on the basis of the results reported by Marshall,[26, 34] the increase of tissue resistance encountered in diseases involving the lung parenchyma (sarcoidosis, pulmonary fibrosis, asthma and kyphoscoliosis) is seldom a major part of the increase in the work of breathing.

Patients with *restrictive lung diseases* or *pulmonary fibrosis* are characterized by a low and relatively stable compliance and a somewhat increased mechanical resistance. There is no significant drop in compliance or resistance with increase in respiratory rate.* This could mean that unequal ventilation is present, but that the time constants of the different pathways are equal, so that the distribution of flow within the lungs remains unchanged. On the other hand, a decrease in lung volume, by thoracic deformity, an intrathoracic space-occupying lesion, or resection, could produce a lowered compliance without a proportionate increase in resistance.

Finally, inflammatory or fibrotic changes in themselves may lead to a decrease in compliance.[7] The patients with pulmonary fibrosis show the lowest value for compliance per liter of vital capacity.

Cardiacs: The cardiac group shows essentially the same features as do the patients with pulmonary fibrosis or restrictive lung disease. Resting compliance is low, but it often shows a further drop during hyperventilation. The resistance values are higher than normal. No consistent correlation could be found in this group between compliance and either pulmonary hypertension, pulmonary blood flow or resistance to pulmonary blood flow (figure 2). A normal compliance was expected in cases 79 and 81 because they had systemic arterial disease without heart failure or pulmonary congestion. The relatively high compliance in cases 99 and 100 can be explained by the presence of chronic pulmonary emphysema in asssociation with mitral stenosis. If these four cases are not considered, the mean compliance of the group drops to 0.07 L/cm. H_2O, and the compliance per liter vital capacity to 0.032 L/cm. H_2O.

* Superimposed emphysema or bronchitic changes may account for the few cases in whom a frequency-dependent compliance is present. These cases also show the highest resistance values.

One is again confronted with the question of whether the reduction of compliance in these cases is due to unequal ventilation, to vascular engorgement per se, or to fibrosis. Fibrosis appears to be less frequently found, even in long-standing mitral stenosis, than was previously thought.[35] A drop in compliance from 0.218 to 0.100 L/cm. H_2O in 11 subjects was reported when the central venous pressure was raised 27 cm. H_2O by inflation of a G suit.[36] However, it is not clear whether the reported changes were due to increased vascular pressures or to decreased lung volumes. In dogs, acute changes of pulmonary blood volume are followed by compliance changes.[37] The drop of compliance occurring in normal subjects with a change from the sitting to the supine body position, and the rise of compliance after removal of intrapleural fluid,[27] would also seem to indicate that an increased intrathoracic blood volume might be a factor in the reduction of compliance in these patients, though changes in lung volume probably play an important role under these circumstances. The better correlation between vital capacity and compliance as compared to the correlation between compliance and pulmonary hemodynamics (figures 2 and 3) could mean that compliance is more dependent upon changes in lung volumes than upon changes in pulmonary hemodynamics. On the basis of our results, we were unable to determine which of the above discussed factors are actually responsible for the observed changes in compliance.

The increase in mechanical resistance could be due to a change in tissue viscosity, to hyperemic changes within the bronchial tree, or to a decreased functional residual capacity. Brown et al.[19] attributed the increased mechanical resistance in patients with heart disease to an increase in resistance to air flow. However, they found the increased resistance a variable phenomenon in their group of patients, and therefore related exertional dyspnea to the reduction in vital capacity and altered elastic properties of the lung. Marshall et al.[18] also found that the increase in the work of breathing is due mainly to an increase in elastic resistance. However, Hayward and Knott [20] found no relationship between the degree of dyspnea and the pulmonary rigidity, and attributed the decreased exercise tolerance in these patients to decreased muscular efficiency.

Although vital capacity is closely related to compliance,[1, 4, 19, 21] the correlation between mechanical resistance and vital capacity or maximal breathing capacity is much poorer (figure 3). In general, a high vital capacity and a high maximal breathing capacity are associated with low resistance values. Vital capacity depends upon the size of the lung and is a static measurement. Therefore, a correlation with static compliance would be expected. The maximal breathing capacity, however, is not only a function of the resistance to air flow, but also depends very much upon the muscular effort developed by the subject. A well trained individual can therefore develop high flow rates in spite of an increased mechanical resistance, whereas a chronically ill and weak patient will be unable to achieve a satisfactory maximal breathing capacity in spite of a low air flow resistance.

The wide variation of the air velocity index,[38] even in our normal subjects (which is due in part to the poor predictability of normal maximal breathing capacity values [39]), makes the clinical significance of this index rather doubtful. Correspondingly, there is a poor correlation with mechanical resistance, compliance or the over-all time constant of the lung (compliance times resistance).

On the basis of these results, it would seem that the vital capacity is a rough indication of the elastic properties of the lung in all groups except the chronic pulmonary emphysema group. The actual measurement of mechanical resistance, however, is the only way to obtain information on the flow-resistive properties of the lung. The maximal breathing capacity gives valuable information about the over-all ventilatory function, but by itself is not a measure of flow resistance. *Only in the presence of increased mechanical resistance can a low maximal breathing capacity be interpreted as indicative of bronchial obstruction.*

The increase of inspiratory *and* expiratory resistance, though often disproportional in patients with cardiopulmonary disease, indicates that the maximal breathing capacity is a better test for the over-all ventilatory function than is timed vital capacity, because the maximal breathing capacity includes a series of inspiratory and expiratory phases. The timed vital capacity depends not only on muscular efficiency and mechanical resistance but also to a great extent upon pulmonary compliance. The latter varies from maximal inflation to maximal deflation.[9, 40] In addition, the low static compliance in emphysema promotes ball valving.[8] These two factors interfere with normal emptying from the maximal inspiratory position. In contrast to the timed vital capacity, maximal breathing capacity is performed in the optimal breathing range, i.e., from a high midposition. Higher intrapleural negativity associated with larger lung volumes tends to increase the diameter of the tracheobronchial tree, thereby decreasing mechanical resistance. This is indicated by the resistance values of Dubois,[8] which are the lowest values reported. They have been measured with the patients panting. Under these conditions, ball valving is less likely to occur. Even a lung with high compliance retains some recoil in the inflated stage, thereby applying a counterforce to the highly positive alveolar pressures associated with the high expiratory flow rates of maximal hyperventilation. Though this counterforce may not be sufficient, it puts the ventilatory mechanism in a more efficient and more physiologic position than does the timed vital capacity maneuver, which requires rapid pulmonary emptying over the whole vital capacity range. Though theoretically the best of the simple ventilation tests, the maximal breathing capacity in practical application is unfortunately hampered by the strain it imposes upon the patient.

Summary

1. Compliance and mechanical resistance have been measured during quiet breathing and voluntary hyperventilation in 25 normal subjects, 26 pa-

tients with chronic pulmonary emphysema, 10 with chronic bronchial asthma, 10 with restrictive pulmonary disease, five with pulmonary fibrosis, two with bronchitis, and 22 with cardiovascular disease.

2. These values are significantly different in the normal and the patient groups.

3. Patients with bronchospastic disease are characterized by a drop of compliance with increase in respiratory rate and markedly elevated values for mechanical resistance. The expiratory resistance is often increased out of proportion in comparison to the increase of inspiratory resistance. In some of the emphysematous patients, the physiologic disturbances within the parenchymal structures (loss of elasticity) seem to predominate over the bronchospastic component of the disease.

4. Patients with either restrictive or fibrotic pulmonary diseases are characterized by low and relatively stable compliance values. The resistance values are less elevated than in the bronchospastic group.

5. Patients with cardiac disease show changes similar to those in the pulmonary fibrotic group.

6. Some of the factors which might be involved in these changes are discussed.

7. Compliance correlates well with vital capacity in all groups with the exception of the emphysema group. High vital capacity and maximal breathing capacity are usually associated with low resistance values. The air velocity index correlates poorly with either compliance, mechanical resistance or the over-all time constant of the lung.

8. The results are briefly discussed with regard to the maximal breathing capacity and timed vital capacity tests.

Summario in Interlingua

Vinti-cinque subjectos normal e 75 patientes esseva studiate in stato basal e position decubital. Esseva obtenite registrationes continue del pressiones transpulmonar, del intensitate del instantanee fluxo de aere, e del volumine del aere currente. Le tension elastic del pulmon e le valor medie del resistentia mechanic sub conditiones de inspiration e de expiration esseva determinate in ventilation calme e in hyperventilation a effortio voluntari per medio del technica a ballon esophagee. Le capacitate vital e le capacitate respiratori maximal esseva mesurate le mesme die. Le formula predictori de Baldwin [28] esseva usate pro calcular le indice del velocitate del aere. In plus, le patientes cardiac esseva subjicite a catheterisation dexterocardiac o cardiac combinate.*

Le tension elastic e le resistentia mechanic differe significativemente inter le gruppo normal e le varie gruppos pathologic. Patientes con morbo bronchospastic es characterisate per un reduction del tension elastic sub conditiones de respiration accelerate e per valores marcatemente elevate del resistentia mechanic. Le resistentia expiratori es frequentemente augmentate de maniera disproportionate in comparation con le augmento del resistentia inspiratori. In alicunes del patientes emphysematose le disturbationes physiologic intra le structuras parenchymal (perdita de elasticitate)

* Le studios de catheterisation esseva executate per Dr. J. Dow in le Laboratorios pro le Studio del Circulation al Hospital del Citate de Boston. Un plus detaliate reporto relative a iste patientes va esser publicate alterubi.[29]

pare predominar super le componente bronchospastic del morbo. Patientes con restrictive o con fibrotic morbo pulmonar es characterisate per basse e relativemente stabile valores del tension elastic. Le valores del resistentia es minus elevate que in le gruppo bronchospastic. Patientes con morbo cardiac exhibi alterationes simile a illos incontrate in le gruppo pulmono-fibrotic. Le tension elastic es ben correlationate con le capacitate vital in omne le varie gruppos, excepte le gruppo con emphysema. Alte valores del capacitate vital e del capacitate respiratori maximal es usualmente associate con basse valores de resistentia. Le indice del velocitate del aere se correlationa pauco ben con le tension elastic, con le resistentia mechanic, o con le constante de tempore general del pulmon.

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SURGICAL THERAPY FOR CHRONIC NONSPECIFIC PNEUMONITIS *

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In 1948 Kershner and Adams [4] introduced the term "chronic nonspecific pneumonitis" to describe a definite pulmonary lesion that had several characteristics. Clinically, this lesion provoked a febrile illness with an insidious onset, chronic course, productive cough, pleuritic pain, and occasionally hemoptysis. Pathologically, the involved area, usually limited to a lobe, was heavy and fibrotic. Microscopic examination showed intralobular and interalveolar fibrosis, thickening of the alveolar walls, lymphoid and plasma cell hyperplasia, redundance of the bronchial mucosa, chronic atelectasis, and hemorrhagic and purulent alveolar exudate. Kershner and Adams reported on the surgical treatment of 10 such cases, all of whom had been incapacitated by the disease. Three of the 10 cases were treated by drainage, seven by resection. Results were good in eight of the cases; one case of drainage (essentially biopsy) remained unchanged, one case treated by pneumonectomy died. It was recommended that when the diagnosis of chronic nonspecific pneumonitis could be made, resection should be the therapy of choice. At the same meeting (American Association of Thoracic Surgery), Brewer, Jones and Dolley,[2] in reporting on various pulmonary lesions removed with the suspected preoperative diagnosis of bronchogenic cancer, mentioned three cases of chronic pneumonitis. Each of the three was cured by resection, and the authors remarked: "These conditions (that is, chronic pneumonitis) are rare and no criterion for diagnosis and treatment has been established."

The following year Waddell, Sniffen and Sweet [6] reported treating 10 cases of chronic pneumonitis by pulmonary resection. These authors noted a large amount of cholesterol in each of the resected specimens, and attributed the disease to the cholesterol, although admitting the mechanism was in doubt. In 1951 Ashe, McDonald and Clagett [1] reported a single case of chronic pneumonitis cured by pulmonary resection. (This case was of interest in that it simulated a superior sulcus tumor.) There are probably many more cases buried in the literature under other titles. For example, Davis, Peabody and Katz,[3] in describing 115 cases of "coin lesions," mentioned four cases of chronic pneumonitis that were resected for diagnosis. (This is an accepted procedure and is not for discussion in this paper.) Further, chronic pneumonitis associated with atelectasis resulting from

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bronchial obstruction as seen in the middle lobe syndrome forms a distinct entity that has been reported many times, and is entirely separate from the lesion under discussion.

MacQuigg [5] has recently written a thought-provoking article likewise advocating pulmonary resection as the treatment of choice for chronic or recurrent pneumonitis that does not yield to antibiotic therapy. He skillfully develops the theory that the disease starts as a chronic, and usually localized, bronchitis or bronchiolitis, subsequently to develop metaplasia and bronchiolar fibrosis. He believes that such cases, without the use of antibiotics, would probably have developed into typical bronchiectasis. While the validity of this reasoning cannot be borne out experimentally, the following successful clinical cases would seem to indicate that resection may be the treatment of choice for chronic, nonspecific pneumonitis.

Case Reports

Case 1. A 48 year old man had a six-month history of productive cough, weight loss and chest pain, all following an acute febrile illness diagnosed as virus pneumonia. He had received therapeutic trials with several antibiotics, each of which would partially relieve his symptoms, but he was never free of cough. Occasionally he spat up a small amount of fresh blood. A chest x-ray showed a feathery density in the area of the superior segment of the left lower lobe (figure 1). Bronchoscopy showed an inflammatory reaction in the left lower bronchus, with a small amount of purulent sputum. Bronchography was unsatisfactory. Bacteriologic studies revealed no specific organism. The diagnosis of probable abscess was made and, in view of the therapeutic failure of the antibiotics, the patient was referred for surgical therapy. At thoracotomy the superior segment of the left lower lobe was found to be fibrotic and densely adherent to the contiguous tissues. Segmentectomy was performed. The postoperative course was benign; he left the hospital on the eighth postoperative day and returned to his occupation of carpenter within the month. He has remained well now for four years. Microscopic study of the segment revealed diffuse interstitial fibrosis with intense lymphocytic infiltration, but no evidence of an abscess. Diagnosis: chronic pneumonitis.

Comment: This patient, the first to be operated on in this series, was subjected to operation with the clinical diagnosis of lung abscess. Although the diagnosis proved wrong, the treatment seemed to be correct. The specimen showed typical pneumonitis with fibrosis.

Case 2. A 52 year old woman noted in December the onset of right-sided chest pain, loss of energy, and a general feeling of tiredness. Some two months later she had an episode of paroxysmal coughing and expectorated some mucus and blood, and was immediately hospitalized. Physical examination was negative, but roentgenograms of the chest showed a middle lobe infiltration, thought to be pneumonitis (figure 2A). Cytologic and bacteriologic studies of the sputum were negative. The patient was in the hospital for two weeks, receiving antibiotic and acrosol therapy, with some improvement. After discharge she continued to cough, occasionally getting up a little purulent sputum. Two weeks after discharge x-rays showed an increase in the previously noted density, and she was re-admitted. Bronchoscopy and bronchography were negative, as were cytologic studies of the bronchial washings. The diagnosis of chronic pneumonitis was re-affirmed, and the patient was

discharged on an antibiotic. For five months she continued to feel ill, to cough, and to have pain in her right hemithorax; she finally was unable to carry on with her work, and was re-admitted for surgical therapy. At thoracotomy, many adhesions were present between the middle lobe and the chest wall. The lobe itself was quite fibrotic, but there was no dominant mass. Middle lobectomy was performed. The postoperative course was uncomplicated, and the patient returned to work in a little less than a month. Since then she has done beautifully; she has gained weight, has

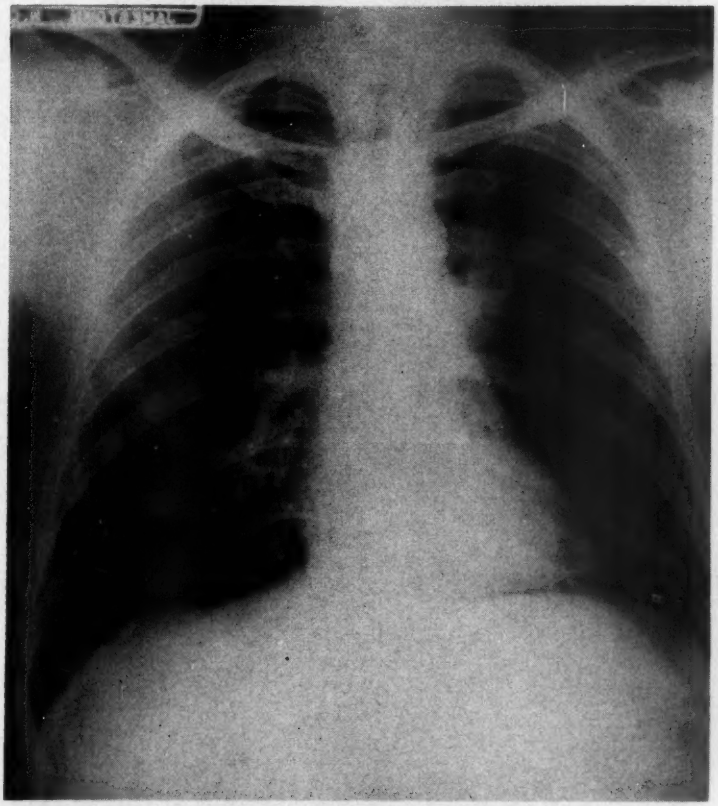

FIG. 1. Chest x-ray showing a feathery density extending up and out from the left hilar region.

no cough, and has felt well. Microscopic study of the specimen revealed dense areas of lymphocytic infiltration, particularly peribronchially (figure 2B). Diagnosis: chronic pneumonitis.

Comment: This patient's internist had urged resection early, but it was only after her disease became painfully drawn out that I agreed to excisional therapy for chronic pneumonitis. The pathologic specimen showed typical chronic pneumonitis. She has been an excellent endorsement of surgical therapy for chronic pneumonitis.

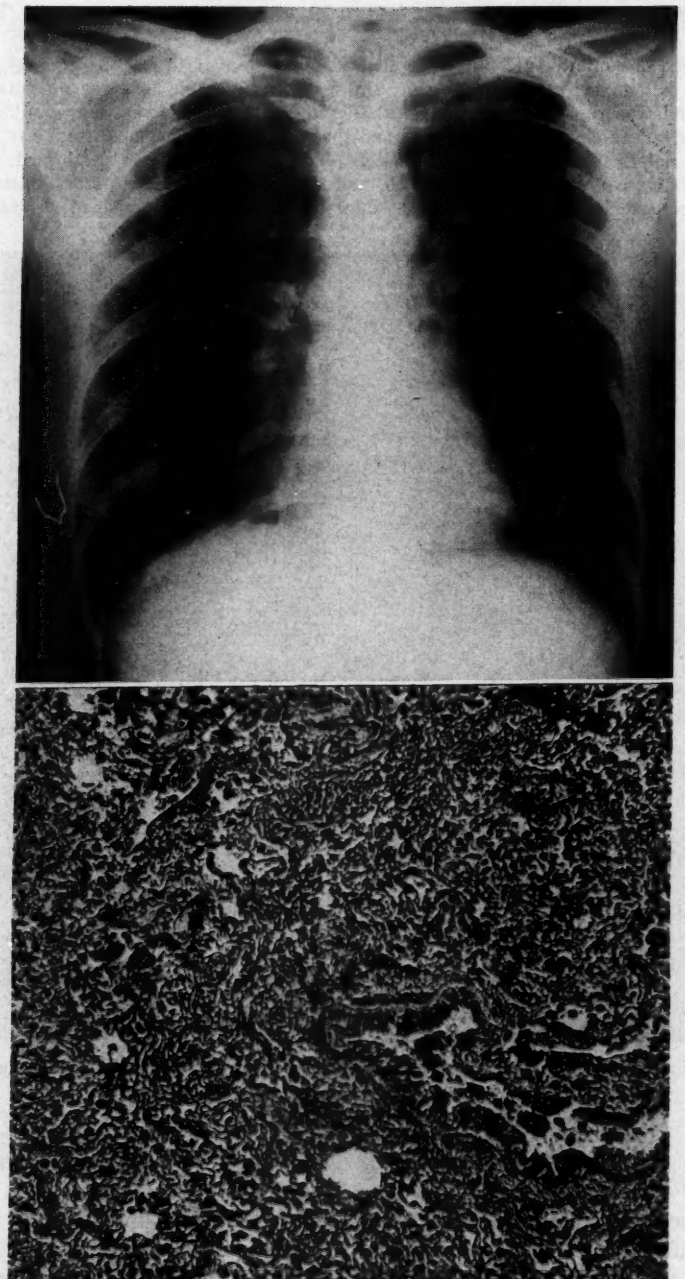

FIG. 2. A (*above*). Chest x-ray illustrating the density in the lateral segment of the right middle lobe. B (*below*). Photomicrograph, 130 ×. Microscopic section showing fibrosis, lymphocytic infiltration (particularly peribronchial), atelectasis.

Case 3. A 58 year old man complained of being weak, listless and tired, associated with a loss of appetite and weight. A complete physical examination revealed no specific abnormality, but a chest x-ray showed consolidation and/or atelectasis of the lateral segment of the middle lobe (figure 3). Treatment with various antibiotics made him feel somewhat better and increased his appetite, but did not alter the roentgenographic findings. Bronchoscopy and bronchography were performed without shedding any light as to the cause of the lesion. It was believed that the density was probably chronic pneumonitis, but since a neoplasm could not be ruled out

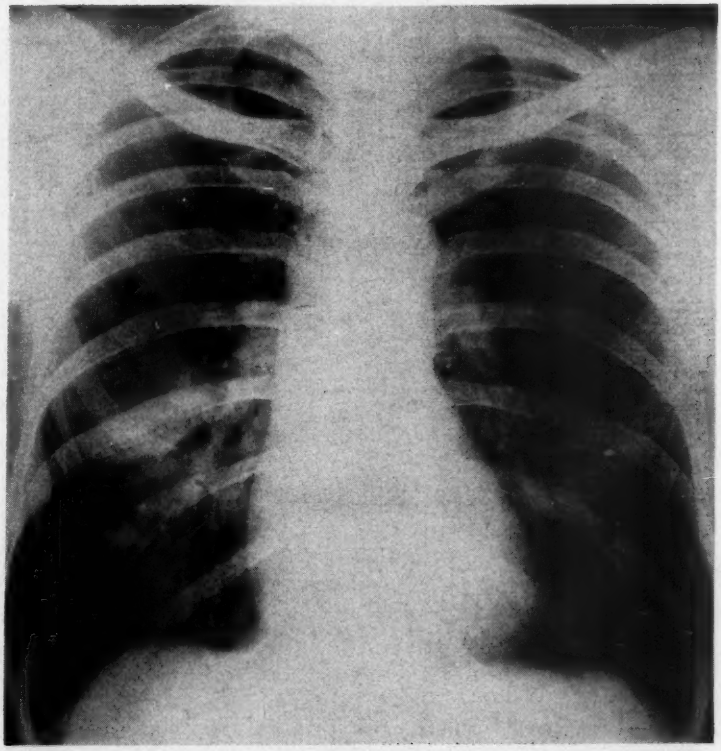

FIG. 3. Chest x-ray, interpreted as showing consolidation and/or atelectasis of the lateral segment of the right middle lobe.

excisional therapy was decided upon. At thoracotomy the lateral segment of the middle lobe was atelectatic, and both segments were rather firm. Middle lobectomy was performed. The patient's recovery was remarkable in that he left the hospital on the sixth postoperative day and returned to work in three weeks. He voluntarily stated, some eight months postoperatively: "I haven't felt this good since I was a boy." Minute examination of the specimen revealed no bronchial cause of the atelectasis. Microscopic examination showed fibrosis, collapse and obliteration of the alveoli, marked infiltration of lymphocytes with occasional foci of plasma cells, focal ulceration of the bronchial mucosa, and bronchial exudate of neutrophils. The

pathologic diagnosis was chronic pneumonitis with acute and chronic bronchitis, and minimal bronchiectasis.

Comment: This patient was operated on because of the possibility of neoplasm. Although the diagnosis was erroneous he was cured by the resection and has remained in good health since then.

Case 4. A 51 year old man whose illness had begun with chills and fever, pain in the right side of the chest, and cough productive of sputum occasionally streaked with blood, was hospitalized and a diagnosis of middle lobe pneumonia was made

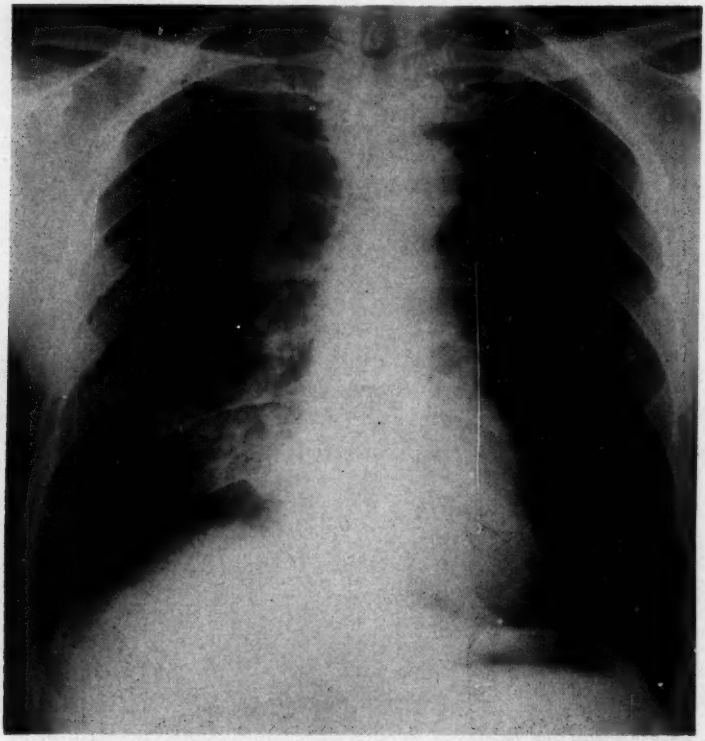

FIG. 4. Chest x-ray, showing consolidation in the right middle lobe area.

clinically and confirmed on x-ray examination (figure 4). With antibiotic therapy he rapidly became afebrile, but continued to have weakness, pleuritic pain and a nonproductive cough. Roentgenographically, the area of consolidation in the right middle lobe remained unchanged. After various antibiotics had been tried over a three-month period with no measurable success, surgical consultation was requested. Physical examination revealed no abnormality. The x-ray appearance of the lesion was unchanged. Bronchoscopy with cytologic and bacteriologic studies of the secretions, and bronchography, revealed no abnormality. Because of the complete lack of improvement since the first week of medical therapy, surgical therapy was advised.

At operation the middle lobe was found to be partially atelectatic, with dense adhesions to all contiguous tissue. The middle lobe was removed. Postoperatively the patient recuperated rapidly, and returned to work in four weeks. In the year since then he has not had any respiratory infections.

Gross dissection of all bronchi and bronchioles revealed no obstruction of the lumen to account for the atelectasis. Microscopic examination revealed thickening of the interalveolar septa, peribronchial fibrosis, and interstitial infiltration of lymphocytes. The diagnosis was chronic pneumonitis and bronchitis.

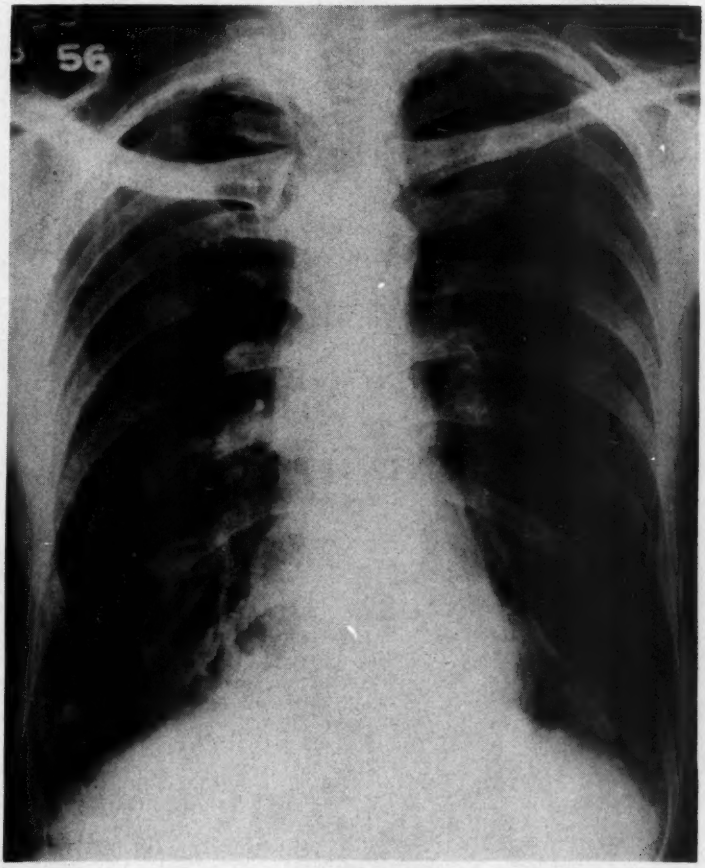

FIG. 5A. Chest x-ray, showing the stringy, ill-defined density in the lateral portion of the right lower lobe.

Comment: By the time this patient was seen it was becoming evident that resection would cure chronic pneumonitis, and might be the treatment of choice. Resection was thus advised, with the preoperative diagnosis of chronic pneumonitis. The result has been highly satisfactory.

FIG. 5. B (*left*) and C (*right*). Photomicrographs, 130 × and 480 ×, demonstrating interalveolar and interstitial fibrosis, edema, lymphocytic infiltration and focal ulceration of the bronchi.

Case 5. This 66 year old farmer was admitted with a five-month history of cough and weight loss (30 pounds). He had had several episodes of "feeling bad all over," accompanied by right-sided chest pain, cough occasionally productive of phlegm, and loss of appetite. For each episode he had been treated with a different antibiotic, and seemed to get better only to relapse in a week or two. A miniature x-ray taken six weeks after the onset of the illness was said to have been negative. A full-size chest plate taken just before admission showed a stringy, ill-defined density in the right lower lobe (figure 5 A). Physical examination showed a tall, gaunt man with bronchial breathing over the right lower lung area. Bronchoscopy

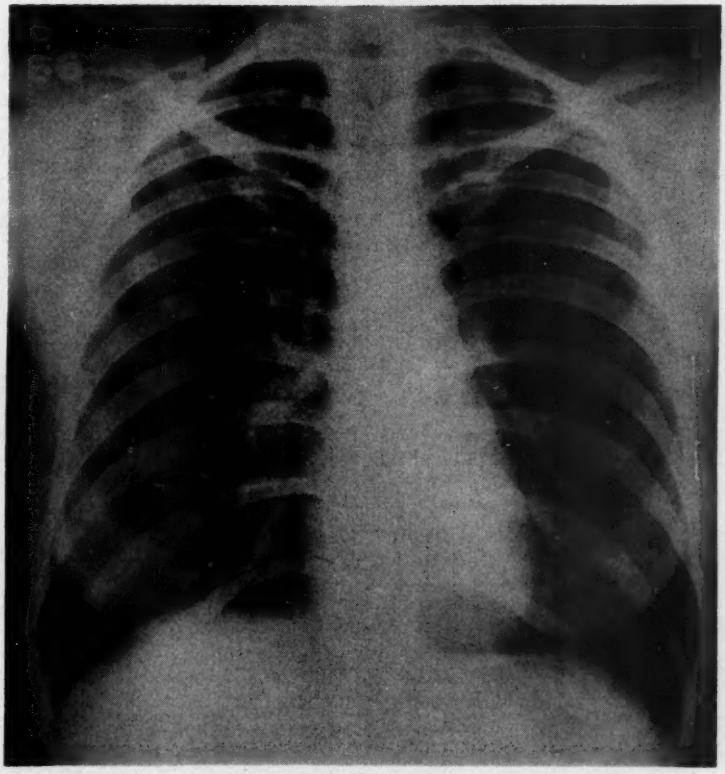

FIG. 6. Chest x-ray. Notice increased linear density extending down from the right hilar area.

showed reddening of the right lower lobe bronchus. Bronchography showed poor filling in the area of the lesion, although adequate contrast medium was present in the larger bronchi. Cytologic and bacteriologic studies on the bronchial secretions were negative. It was believed that this man probably had chronic pneumonitis, but the possibility of a neoplasm could not be ruled out. Regardless of the etiology, excisional therapy was thought to be indicated because of the disabling chronicity of the process. At thoracotomy there was some puckering of the visceral pleura over the lower lobe, and a diffuse mass was palpated thereunder. Lobectomy was

performed. The patient's discharge from the hospital was delayed until the twelfth postoperative day by an early, persistent air leak, but his convalescence was otherwise uneventful. He has remained in excellent health for the nine months since operation, and has regained his weight. Microscopic sections of the involved portions of the lower lobe showed interalveolar and interstitial fibrosis, edema, lymphocytic infiltration and focal ulceration of the bronchi (figures 5 B and C). No obstruction of the bronchi could be demonstrated. Diagnosis: chronic pneumonitis and bronchitis.

Comment: This patient was the oldest in the series, and his case is strong evidence in favor of resection despite age. Undoubtedly the suspicion of cancer augmented our belief that resection was indicated, but postoperatively it was evident that chronic pneumonitis was sufficient indication for operation, even in this case.

Case 6. This 40 year old widow entered the hospital with a complaint of "colds all winter," the colds being characterized by cough (occasionally productive of purulent sputum), fever, chills and pleuritic pain. She had been treated almost constantly with antibiotics and antihistamines, each new one being tried as it appeared, without noticeable benefit. Physical examination showed a thin, tired looking woman who coughed frequently and who looked somewhat older than her stated age; otherwise the examination was negative. Roentgenographic examination showed an area of density just at and below the right hilar area; this was interpreted as atelectasis and/or pneumonitis (figure 6). Bronchoscopy revealed no abnormality. Bronchograms revealed minimal beading of the middle lobe bronchi and a lack of filling that is usually seen with retained secretions. Bacteriologic sensitivity studies were carried out on the sputum flora, and the patient was treated for three weeks with the indicated antibiotic. There were no changes in the symptoms or x-ray findings. Excisional therapy was decided upon. At operation the lung appeared to be normal, but palpation of the middle lobe revealed it to be quite firm. Middle lobectomy was performed. The patient's recovery was uneventful and she was discharged on the twelfth postoperative day. She immediately began to gain weight, stated she felt much better, and in a little over six months married again. Microscopic examination of the specimen showed thickening and hyalinization of the bronchiolar basement membranes, peribronchial infiltration of lymphocytes and plasma cells, and interstitial lymphocytic infiltration. Diagnosis: chronic pneumonitis and bronchitis.

Comment: This patient was the youngest in the series. I was extremely reluctant to suggest operative therapy, as her husband had had cancer of the lung and had died following exploratory thoracotomy (by myself) only six months earlier. However, she was desperate and anxious to try anything that offered possible relief. Her recovery was quite gratifying.

Conclusions

Chronic nonspecific pneumonitis is a definite entity that can be diagnosed clinically and roentgenographically. The initial treatment should be medical. For those cases that fail to respond to intensive medical therapy, or that recur promptly when medical therapy is discontinued, pulmonary resection becomes the treatment of choice.

SUMMARIO IN INTERLINGUA

In 1948, le termino "pneumonitis nonspecific chronic" esseva introducite per Kershner e Adams pro describer un definite entitate pulmonar. Ab le puncto de vista clinic, le lesion in question provocava un morbo febril con declaration insidiose, curso chronic, tusse productive, dolor pleuritic, e in certe casos hemoptysis. Ab le puncto de vista del pathologia, le area interessate esseva usualmente limitate a un lobo e exhibiva fibrosis intralobular e interalveolar, spissification del parietes alveolar, hyperplasia del cellulas lymphoide e plasmatic, redundantia del mucosa bronchial, atelectasis chronic, e hemorrhagic e purulente exsudato alveolar. Esseva monstrate que le extirpation del area afficite resultava usualmente in marcate grados de melioration. Depost ille tempore, plure autores ha reportate micre series de patientes in qui simile resultatos esseva obtenite.

MacQuigg ha avantiate le theoria que le morbo comencia como un chronic bronchitis localisate que subsequentemente disveloppa metaplasia e fibrosis bronchiolar. Ille crede que tal casos, si non tractate, se disvelopparea in typic bronchiectasis sed que antibioticos es capace a arrestar iste progression. Il non es possibile provar iste theoria experimentalmente, sed observationes clinic supporta nettemente le recommendation de MacQuigg que resection debe esser considerate como le tractamento de election pro pneumonitis nonspecific chronic.

Es presentate sex historias clinic. Omne iste patientes—con etates de inter 40 e 66 annos—presentava un longe historia de chronic infection pulmonar, con effectuation de un alleviamento partial durante le application de un therapia antibiotic. Roentgenogrammas thoracic esseva positive in omne le casos pro infiltration pulmonar. Isto variava in intensitate ab plumose usque a dense. Le examine physic esseva generalmente pauco interessante, excepte que cata un del patientes esseva apparentemente chronicamente malade. Usualmente le bronchoscopia revelava alterationes incidente a bronchitis chronic. Le bronchogrammas esseva interpretate como normal, excepte que grados minimal de bronchiectasis esseva notate in duo del patientes. Al operation il esseva trovate que le area afficite esseva pesante, fibrotic, e sin aere. Lobectomia esseva executate in cinque casos, segmentectomia in un. Le curso postoperatori esseva sin complicationes in omne iste casos, e omne le patientes retornava a un occupation remunerative.

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SOME METABOLIC FACTORS IN THE TREATMENT OF HYPERTHYROIDISM *

By I. Darin Puppel, M.D., E. K. McCormick, M.S., and E. Herdle, M.S., *Columbus, Ohio*

Our knowledge concerning the influence of calcium, phosphorus and vitamin D administration on hyperthyroidism is as yet meager and, at times, confusing. The exact mechanism of action of calcium and phosphorus and their consequent therapeutic indications in the management of patients with hyperthyroidism are not fully understood, despite the fact that calcium has been employed in this condition by experienced clinicians, including Theodore Kocher, for many years.[44, 51, 7, 41] In fact, certain investigators [27, 28] have expressed doubt that added calcium would be beneficial in counteracting the negative calcium balance of this disease, although their investigations had not extended this far. Wherever possible, rational drug therapy should be based upon a correlation of the pharmacodynamic action of the drug with the pathologic physiology of the disease. It seemed essential from a therapeutic standpoint to determine whether positive calcium and phosphorus balance could be maintained by high calcium, phosphorus and vitamin D intake.

The gross disturbances of calcium and phosphorus metabolism (figures 1, 2, tables 1, 2), which exist in hyperthyroidism usually consist principally of an increased excretion of calcium and phosphorus through both the gastrointestinal and urinary systems [27, 28, 6] (tables 1, 2). The blood calcium and phosphorus usually remain within normal limits [6, 56, 67] (figures 1, 2). The blood phosphatase is usually slightly increased (figures 3, 4). These abnormal findings differ greatly from those in hyperparathyroidism, in which the increased excretion usually occurs almost quantitatively through the urine (figures 3, 4), while the blood calcium, phosphorus and phosphatase levels are usually greatly disturbed [10] (figure 3). These abnormalities lead to definite differences in the clinical manifestations of the disturbed calcium and phosphorus metabolism in these two disease entities, which may be of definite therapeutic significance.[68] The real danger in feeding high calcium and phosphorus preoperatively to patients with hyperparathyroidism is that it may increase the predisposition to metastatic calcification. In hyperthyroidism no such danger exists if the renal function is normal.

Patients with exophthalmic goiter excrete more minerals than do those with toxic nodular goiter [6] (figures 1, 2), even when basal metabolic rates are at similar levels [68] (figures 5, 6). However, the state of the calcium

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TABLE 1

The Calcium Balance in Hyperthyroidism: A Comparison of the Calcium Balance of Hyperthyroid Patients with That of Normal Persons and Nontoxic Nodular Goiter Patients

Type of Goiter Present	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Calcium mg. %	Average Output per Three-Day Period			Average Intake per Three-Day Period gm.	Average Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. None: Normal controls	3	30	−11	10.8	0.437	0.709	1.146	0.913	−0.233
2. Nontoxic nodular	2	18	− 9	10.5	0.428	0.859	1.287	1.079	−0.208
3. Toxic nodular	3	21	+32	10.8	0.355	1.174	1.529	1.147	−0.383
4. Mixed toxic	1	9	+27	11.4	0.439	1.582	2.021	1.109	−0.912
5. Exophthalmic	7	60	+56	11.0	0.985	2.376	3.361	1.567	−1.794

balance is not wholly independent of the degree of hyperthyroidism. In patients with nontoxic nodular goiter, the calcium metabolism remains normal (figure 1).

In hyperthyroidism these metabolic disturbances vary greatly, are usually temporary, preventable and reversible in character, and may easily be prevented or corrected by oral or parenteral administration of extra amounts of calcium and phosphorus, as will be seen presently (figures 7, 8). Ingestion of milk, with its high calcium and phosphorus content, leads to calcium and phosphorus retention. The state of the calcium and phosphorus balance in hyperthyroidism is therefore dependent to a great extent on the actual calcium and phosphorus content of the diet. If iodine administration returns the basal metabolic rate toward normal, one may expect a decrease in the calcium and phosphorus excretion.[67] Parenteral administration of calcium (figure 7), thyroidectomy [67] or thiouracil [74] may also produce a positive balance.

Various experimental and clinical demonstrations of gross disturbances of calcium and phosphorus metabolism in hyperthyroidism have also been

TABLE 2

The Phosphorus Balance in Hyperthyroidism: A Comparison of the Phosphorus Balance of Hyperthyroid Patients with That of Normal Patients

Type of Goiter Present	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Phosphorus mg. %	Average Output per Three-Day Period			Average Intake per Three-Day Period gm.	Average Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. None: Normal controls	4	48	+ 4	4.4	1.456	0.819	2.275	2.157	−0.118
2. Toxic nodular	1	6	+43	4.0	1.698	1.219	2.917	2.439	−0.478
3. Mixed toxic	1	9	+27	6.6	2.294	1.468	3.763	2.439	−1.324
4. Exophthalmic	3	18	+64	4.2	2.783	1.188	3.971	2.987	−1.005

made by other investigators.[24, 83, 58, 12, 44, 52, 76, 60, 17, 16, 11, 48] However, the mechanism of these disturbances in hyperthyroidism has never been clearly demonstrated.[6, 12, 27, 28, 54, 67, 71, 72, 61] Recent thiouracil studies [74] would tend further to uphold our hypothesis [61] that this increased excretion is due to a combination of factors, underlying which is the increased utilization of the thyroid hormone by the tissues. When thyroid hormone production is decreased, mineral elimination returns toward normal.

Manifestations of the disturbed calcium and phosphorus metabolism in hyperthyroidism are greatly variable. Clinically, they may be absent or so

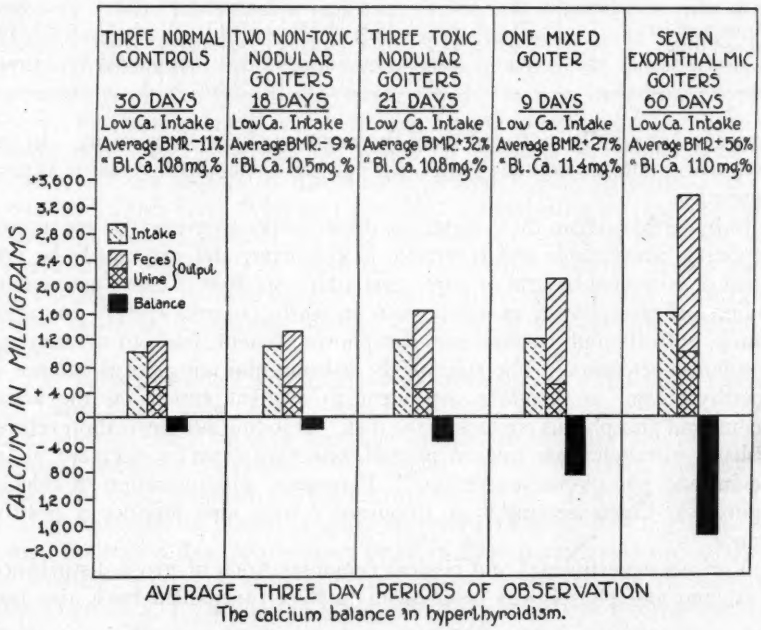


FIG. 1. A comparison of the calcium balance of hyperthyroid patients with that of normal people and of nontoxic nodular goiter patients.

mild that the more predominating toxic symptoms mask them. Painful muscular, joint and bone complaints are frequently encountered.[70, 42, 8, 59, 17, 51, 54, 9, 18, 84, 49] Usually these are mild in character. Severe forms are rather uncommon, and may simulate symptoms of acute post-traumatic bone atrophy. In many instances these have been erroneously diagnosed as a nonspecific and obscure form of arthritis. The first signs are swelling and pain on movement, with subsequent increasing limitation of motion and atrophy of involved muscles. Tenderness, myasthenia, muscle contractures and pseudofixation of joints may occur later. In such cases high calcium and vitamin D feeding, as well as thyroidectomy, has been found to give

definite symptomatic relief, even though roentgenograms did not show evidence of recalcification.[51, 84]

Skeletal decalcification was described by von Recklinghausen in 1891.[70] Many similar reports of bone atrophy have since been made.[42, 3, 59, 45, 34, 76, 51, 18, 4, 50, 33, 19, 23] Kummer [44] in 1917 presented, probably for the first time, radiographic evidence of osteoporosis associated with hyperthyroidism. Roentgenography in the early disease is usually negative, but in advanced

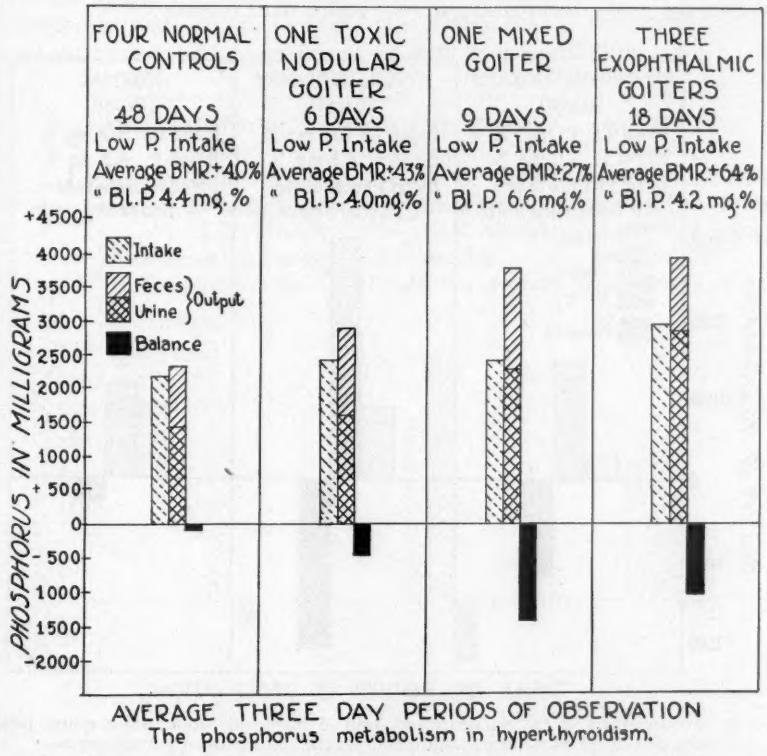


FIG. 2. A comparison of the phosphorus metabolism of hyperthyroid patients with that of normal people.

stages generalized decalcification of the skeleton may be obvious, as has been reported by numerous other observers [13, 59, 23, 17, 9, 18, 84, 6, 34, 49, 76, 57, 25, 77] (figures 11, 12, 13). In a few cases osteoporosis is profound in degree. Osteomalacia has occurred with subsequent gross deformity of the bones and dwarfism.[70, 42, 3, 45, 82, 35, 13, 59, 33, 19] In some cases spontaneous fractures have resulted.[59, 23, 84, 17, 26, 51, 9, 36] Deformity and dwarfism may be due to fractures or severe osteomalacia. Subjective symptoms are often associated.

The severity of these symptoms depends upon the stage, the duration and the complications of the disease at the time of diagnosis, as well as upon the degree of calcium excretion and the amount of calcium intake during the entire course of the disease.

Since early in the nineteenth century an upset of the calcium metabolism has been considered by many a factor in the production of goiter.[61, 29] Investigators have also believed that a disturbance in the calcium metabolism is causally related to some of the toxic symptoms of hyperthyroidism. But not even the gross disturbances were revealed until recently.[6, 61]

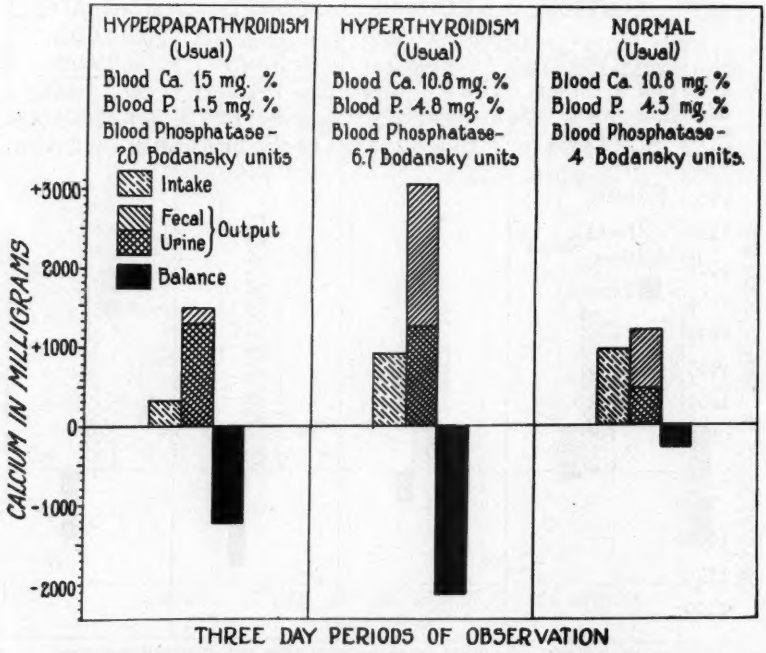


FIG. 3. A comparison of the calcium metabolism of the usual exophthalmic goiter patient with that of the usual hyperparathyroid patient and the usual normal person.

In 1936, while doing iodine and calcium correlation studies, we discovered that one of the patients with hyperthyroidism showed remarkable retention of calcium over normal when enough was given to meet the increased metabolic requirements of the disease.[67] This demonstrated to us the possible need for adequate calcium therapy, and led us to investigate the effects of calcium feeding upon the negative calcium balance of hyperthyroidism. Until that time, it had been believed that ingestion of extra amounts of calcium did not influence the retention of calcium. Since then we have given many of our hyperthyroid patients calcium, phosphorus and vitamin D pre-

operatively. In this respect, it is significant that none of the patients who received an adequate supply of calcium, phosphorus and vitamin D developed so called thyroid crisis, even before the advent of antithyroid drugs and radioiodine therapy. The postoperative reactions have been minimal. There have been no deleterious effects.

Because of the fundamental importance of these clinical factors in the management of certain patients with toxic goiter, we became vitally interested in determining whether administration of adequate amounts of calcium, phosphorus and vitamin D would appreciably change the negative calcium and phosphorus balance of the patient with hyperthyroidism.

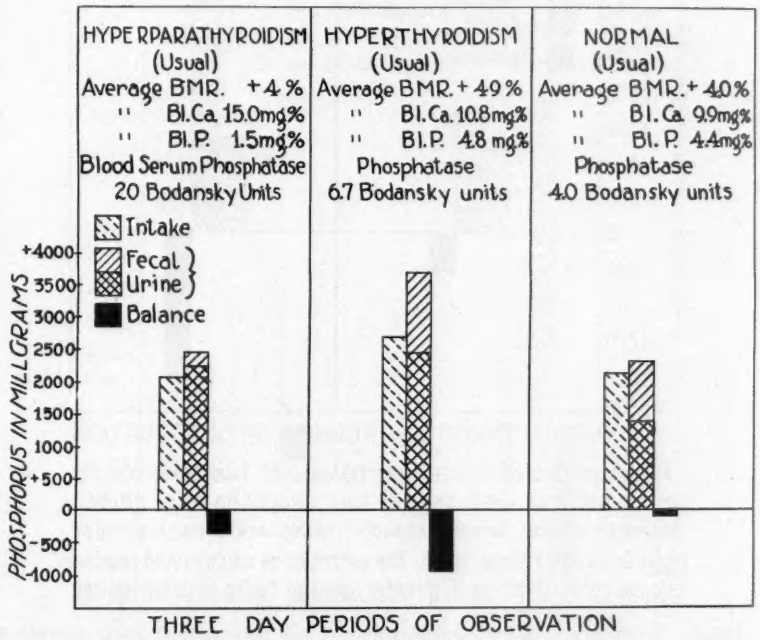


FIG. 4. A comparison of the phosphorus metabolism of the usual exophthalmic goiter patient with that of the usual hyperparathyroid patient and the usual normal person.

EFFECTS OF ADEQUATE CALCIUM, PHOSPHORUS AND VITAMIN D ADMINISTRATION ON THE NEGATIVE CALCIUM AND PHOSPHORUS BALANCE OF HYPERTHYROIDISM: COMMENTS

We have made extensive researches of seven normal people and of 11 patients suffering from toxic goiter over a total period of more than 500 days under great variations of calcium, phosphorus and vitamin D therapy. The principles underlying the clinical and laboratory methods have been set forth in detail in previous papers.[61, 62, 63, 67, 68]

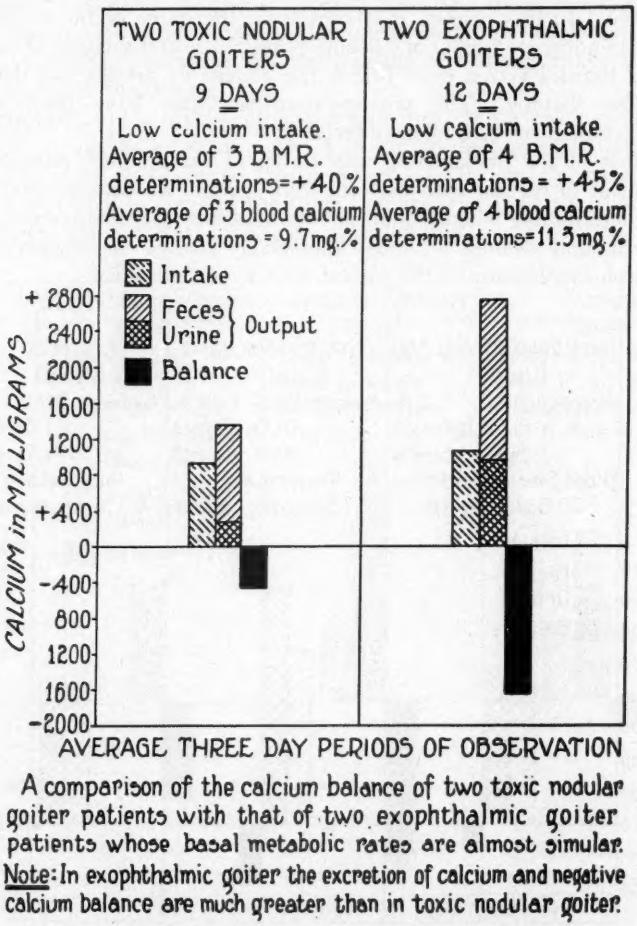


FIG. 5. A comparison of the calcium balance of two toxic nodular goiter patients with that of two exophthalmic goiter patients whose basal metabolic rates are almost similar. *Note:* In exophthalmic goiter the excretion of calcium and the negative calcium balance are much greater than in toxic nodular goiter.

These studies reveal a grave loss (tables 3, 4, figures 7, 8) of calcium and phosphorus on low intake or even on an intake optimal for normal people. Diets of high calcium and phosphorus content due principally to added milk (600 to 1,500 c.c. daily) lead to remarkable retention of both calcium (table 3, figure 7) and phosphorus (table 4, figure 8). We have also supplemented the high calcium and high phosphorus diets with four of the most common types of calcium salt used in therapy. They were all effective in maintaining retention of both elements (tables 3, 4, figures 7, 8).

Eleven hyperthyroid patients maintained on a relatively low intake of calcium (averaging 474 mg. per day over a total period of 90 days) showed an average loss of 459 mg. per day (table 5, figure 9). When five of these patients were investigated on an adequate intake of calcium from different sources (averaging 2,410 mg. per day, but ranging from 1,622 to 3,560 mg. over a total period of 81 days), great retention of calcium resulted (table 5,

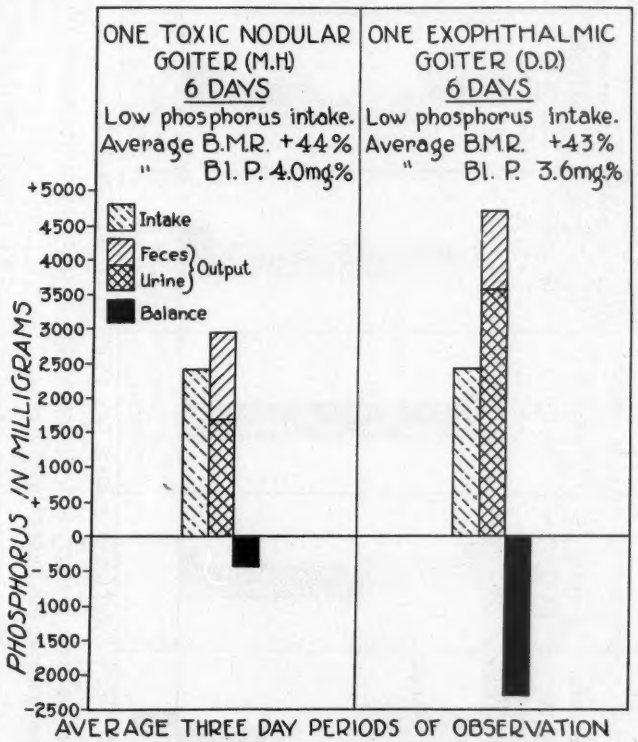
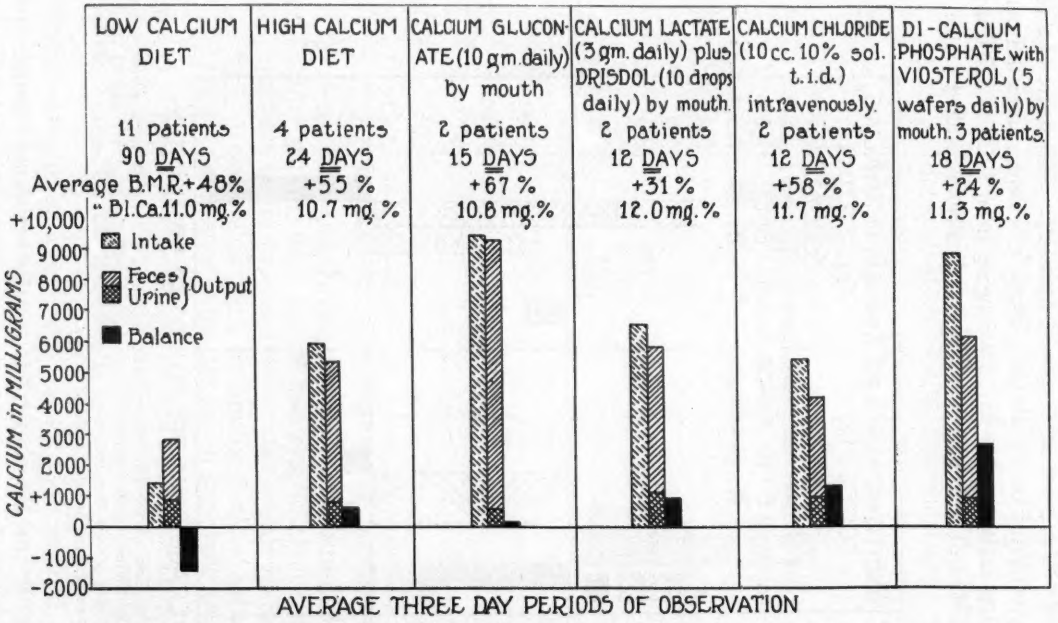


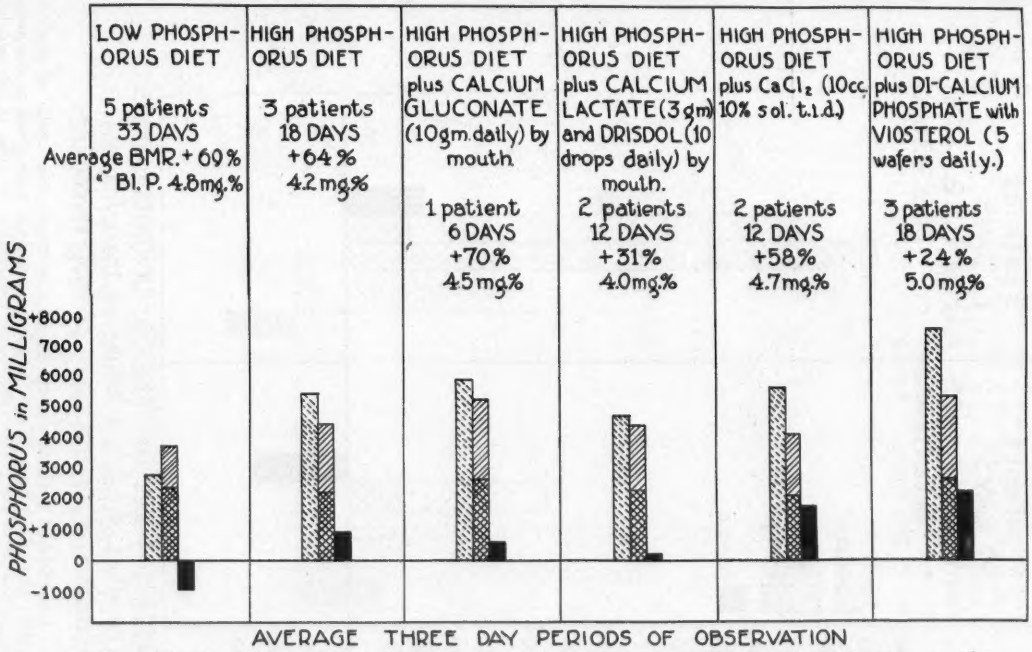
FIG. 6. A comparison of the phosphorus metabolism of a toxic nodular goiter patient with that of an exophthalmic goiter patient whose basal metabolic rates are almost similar. *Note:* In exophthalmic goiter the excretion of phosphorus and the negative phosphorus balance are much greater than in toxic nodular goiter.

figure 9). The state of the phosphorus metabolism showed similar spectacular and beneficial changes (table 6, figure 10). Retention occurred whether the extra calcium was fed or was administered parenterally in the face of severe diarrhea.[68] In our series, wafers of dicalcium phosphate with viosterol were instrumental in producing the most marked retention of calcium when the amount of each drug was administered within reasonable



The effect of calcium feeding and of parenteral calcium administration on the calcium balance of several cases of hyperthyroidism.

FIG. 7. Diets of high calcium and phosphorus content principally due to added milk lead to consistent retention of calcium. We have also supplemented these diets with four of the most common types of calcium salt used in therapy. They were all effective in maintaining retention of calcium. Dicalcium phosphate with viosterol produced the most marked retention of calcium when the drugs were given in palatable doses.



The effect of Phosphorus feeding and of parenteral calcium administration on the phosphorus metabolism of several cases of hyperthyroidism.

FIG. 8. Diets of high calcium and phosphorus content principally due to added milk lead to great retention of phosphorus. We have also supplemented these diets with four of the most common types of calcium salt used in therapy. They were all effective in maintaining retention of phosphorus. Dicalcium phosphate with viosterol also produced the most marked retention of phosphorus. It was of course the only calcium salt which added extra phosphorus to the diet.

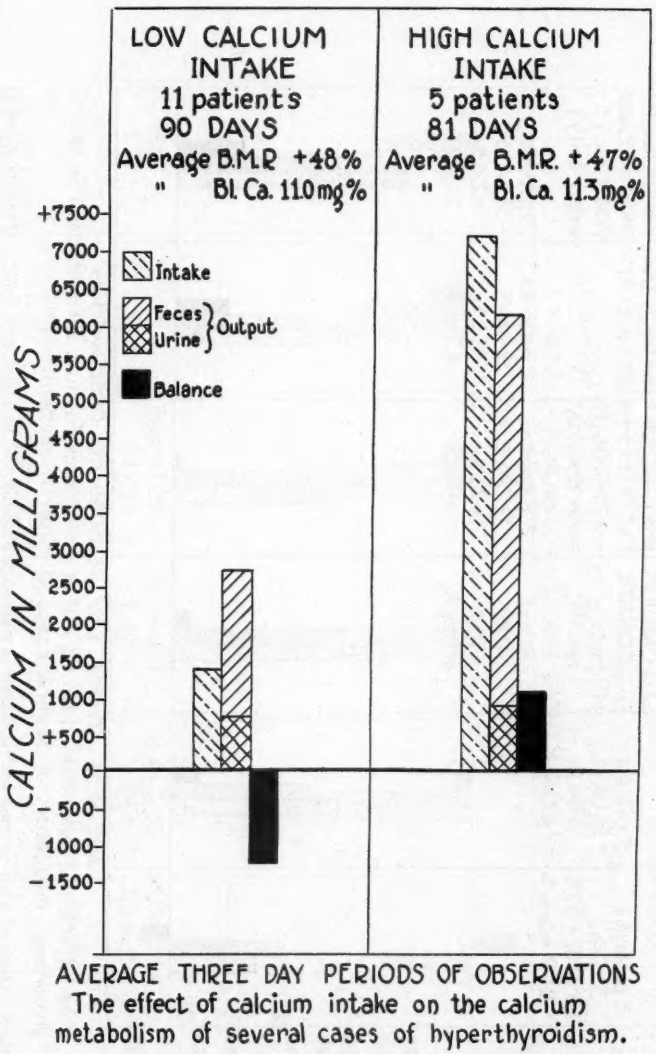


FIG. 9. Eleven hyperthyroid patients maintained on a relatively low intake of calcium and phosphorus showed loss of calcium. When five of these patients were given an adequate intake of calcium and phosphorus from different sources, remarkable retention of the calcium resulted.

limits of palatability (table 3, figure 7). Wafers of dicalcium phosphate with viosterol also produced the greatest retention of phosphorus (table 4, figure 8). Of course, this was the only calcium salt which added extra phosphorus to the diet.

Case Reports

Case 1. A female patient, referred to one of us (I. D. P.), of 52 years with toxic nodular goiter of three years' duration complained of shoulder pain which was excruciating in nature. It simulated that of Sudeck's bone atrophy and required large amounts of morphine. The patient later became bedfast because of severe generalized

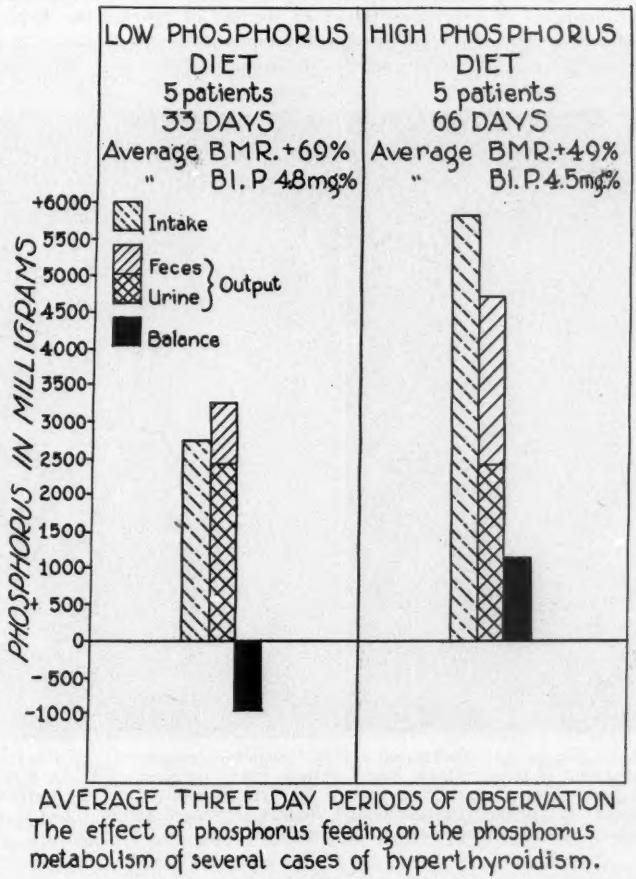


Fig. 10. Eleven hyperthyroid patients maintained on a relatively low intake of calcium and phosphorus showed loss of phosphorus. When five of these patients were given an adequate intake of calcium and phosphorus from different sources, splendid phosphorus retention occurred.

myasthenia. She was still menstruating normally. Administration of adequate amounts of calcium, phosphorus and vitamin D resulted in splendid retention of as high as 2 gm. of calcium (figure 14) and 1.2 gm. of phosphorus (figure 15) daily. She experienced remarkable improvement of symptoms during eight days of adequate calcium, phosphorus and vitamin D therapy, so that she soon required no morphine

and became ambulatory. An x-ray film of the left shoulder, obtained in 1941, before proper treatment of the calcium and phosphorus disturbances, revealed moderately advanced osteoporosis (figure 11-1). A radiogram obtained five years after adequate treatment of the hyperthyroidism and the continued use of proper amounts of calcium, phosphorus and vitamin D showed almost complete restoration of the normal trabecular architecture of the cancellous bone (figure 11-2).

Case 2. A female patient of 61 years was referred to one of us (I. D. P.) with a provisional diagnosis of hyperparathyroidism because of spontaneous kyphosis with dwarfing of four inches, muscular pain, spontaneous pathologic fractures and marked generalized myasthenia. Generalized, far-advanced osteoporosis was easily detected

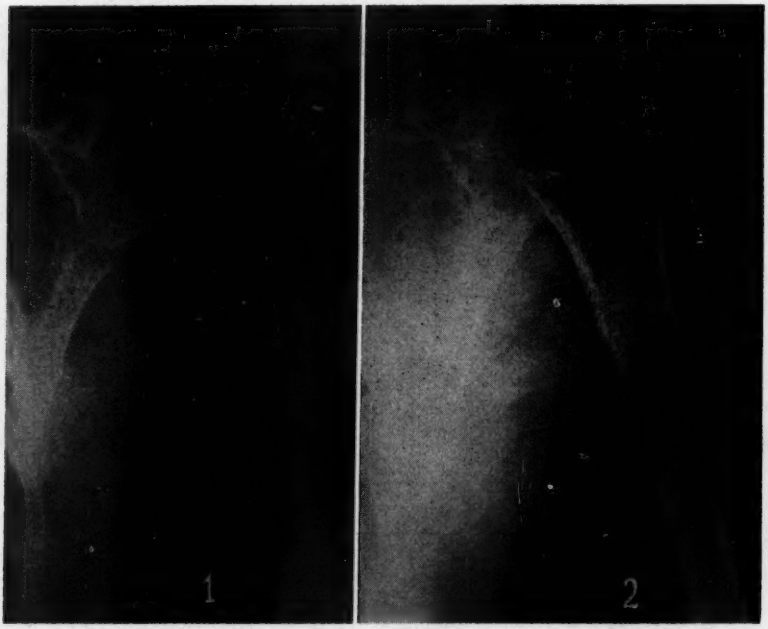


FIG. 11. *Case 1.* (1) Radiogram revealed moderate osteoporosis of the left humerus prior to treatment of toxic nodular goiter of three years' duration. (2) An x-ray film obtained five years after adequate treatment of the hyperthyroidism and the continued use of proper amounts of calcium, phosphorus and vitamin D showed almost complete restoration of the normal trabecular architecture of the cancellous bone.

on the x-ray films (figures 12, 13). Osteomalacia with subsequent compression fractures of several thoracic and lumbar vertebrae had occurred (figure 13). This symptomatology was discovered to be due to toxic nodular goiter of 10 years' duration. The parathyroid function was normal. Great symptomatic relief occurred following adequate calcium, phosphorus and vitamin D therapy, along with thyroidectomy. Since therapy, begun 10 years ago, no other pathologic bone changes and no fractures have occurred.

Case 3. A male patient of 63 years was referred to one of us (I. D. P.) in July, 1954, for investigation of the cause of moderate generalized osteoporosis. He complained of a multiplicity of compression fractures of the spine and of a spontaneous

fracture of a rib. He had had a solitary nodular goiter for 50 years. Careful investigation soon uncovered the presence of an apathetic hyperthyroidism of many years' duration. There was no laboratory evidence of hyperparathyroidism. After extensive investigation the orthopedic surgeon, the radiologist and we felt that many factors contributed to the osteoporosis in this case, including hyperthyroidism, osteoporosis of disuse and an imbalance of the sex hormones. Thyroidectomy, adequate diet including high calcium and high phosphorus intake, a Taylor brace and sex hormone therapy greatly improved his general condition. On September 25, 1954,

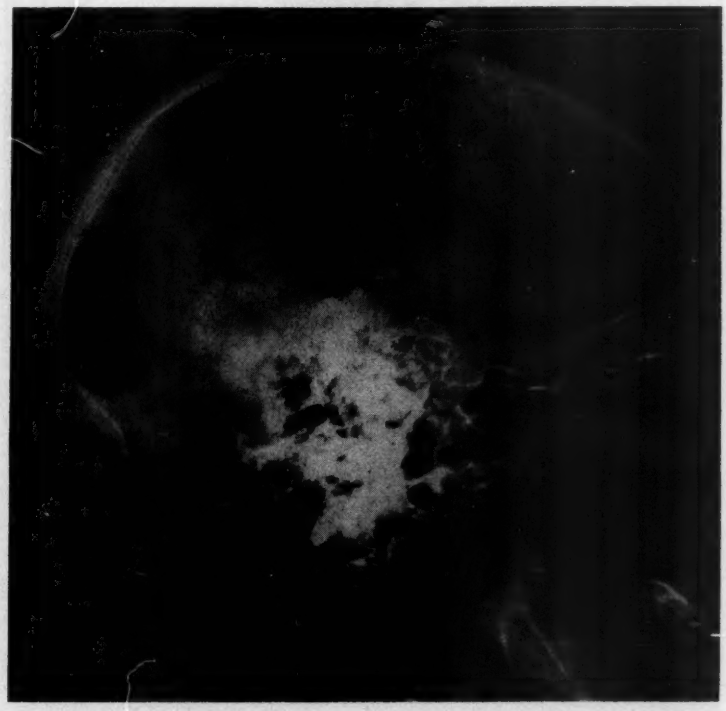


FIG. 12. *Case 2.* There may occur in hyperthyroidism multiple localized areas of osteoporosis which must be differentiated from carcinoma metastatic to bone and from multiple myeloma. The patient was referred to us because of the far advanced generalized skeletal involvement, which was believed to be due to hyperparathyroidism. Careful investigation revealed the osteoporosis to be due to toxic nodular goiter of 10 years' duration.

about three months after surgery, the patient stated that the bone pain had disappeared and that his bones felt stronger. He no longer uses the Taylor brace or receives sex hormone therapy.

Case 4. In November, 1956, one of us (I. D. P.) saw for the first time in surgical consultation a white woman of 69 years. She had a severe, far-advanced toxic nodular goiter with impending thyroid crisis. The protein-bound iodine was 21.4 μg.%, and the blood cholesterol 58 mg.%. With a regimen of bed-rest, sedation, tranquilizers, iodinization, Itrumil, antibiotics, digitalization, blood transfusions and a diet high in protein, carbohydrate, calcium, phosphorus and vitamins, the internists

FIG. 13. The demineralization was here extreme, with softening of bone and subsequent spontaneous compression fractures of several thoracic and lumbar vertebral bodies. Dwarfing of 4 inches, kyphosis, muscular pain and marked generalized myasthenia accompanied. This symptomatology was discovered to be due to toxic nodular goiter of 10 years' duration.

seemingly succeeded in preventing a thyroid crisis. In September, 1955, this patient had been in the same hospital with extremely severe osteoporosis and a multiplicity of fractures of the right humerus, right ulna and right femur following minimal trauma. She had had a goiter for about 40 years and hyperthyroidism for at least 10 years. There was no evidence of hyperparathyroidism. Up to her present illness she had refused thyroidectomy and all medical treatment of her goiter. At present surgery was considered contraindicated, since she was psychotic and mentally agitated. She was greatly emaciated, weighing 60 pounds, with a height of 62 inches. Arterial hypertension and auricular fibrillation were present. The liver function was greatly impaired, with the prothrombin 19%. Gastrointestinal disturbances were

TABLE 3

The Effect of Calcium Feeding and of Parenteral Calcium on the Calcium Balance of Several Cases of Hyperthyroidism

Type of Calcium Intake	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Calcium mg. %	Output per Three-Day Period			Intake per Three-Day Period gm.	Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. Low calcium diet	11	90	+48	11.0	0.784	2.016	2.800	1.423	−1.377
2. High calcium diet	4	24	+55	10.7	0.772	4.540	5.312	5.915	+0.603
3. High calcium diet plus calcium gluconate by mouth (10 gm. daily)	2	15	+67	10.6	0.668	8.669	9.337	9.483	+0.145
4. High calcium diet plus calcium lactate (3 gm. daily) and Drisdol (10 drops daily) by mouth	2	12	+31	12.0	1.044	4.735	5.779	6.547	+0.768
5. High calcium diet plus calcium chloride intravenously (10 c.c. of 10% solution t.i.d.)	2	12	+58	11.7	0.931	3.224	4.155	5.400	+1.255
6. High calcium diet plus dicalcium phosphate with viosterol (5 wafers daily)	3	18	+24	11.3	0.768	5.359	6.127	8.800	+2.673

present, with nausea, vomiting, diarrhea, anorexia and melena. Urinary infection was associated. This patient is continuing to improve slowly on large dosages of propylthiouracil, along with radioiodine therapy.

These brief case reports reëmphasize the fact that nowhere in medicine must we think of the patient as a whole more than in the patient with hyperthyroidism. This disease frequently represents a group of pathologic processes occurring in varying degrees all at the same time.

Without adequate milk or cheese in the diet, it is usually impossible to

obtain through food alone the 2 gm. of calcium required daily by the ordinary hyperthyroid patient. We have found that milk is an excellent source of utilizable calcium and phosphorus for hyperthyroid patients when supplied in quantities of about one and one-half quarts daily. In rare instances diarrhea occurs, so that no milk (or smaller amounts as tolerated) must be given, and other forms of oral or intravenous therapy must be resorted to to supply the deficiency. It must also be remembered that utilization of calcium may be inadequate, even with sufficient intake, unless the factors

TABLE 4

The Effect of Phosphorus Feeding and of Parenteral Calcium on the Phosphorus Metabolism of Several Cases of Hyperthyroidism

Type of Phosphorus Intake	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Phosphorus mg. %	Average Output per Three-Day Period			Average Intake per Three-Day Period gm.	Average Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. Low phosphorus diet	5	33	+69	4.8	2.453	1.270	3.722	2.738	−0.984
2. High phosphorus diet	3	18	+64	4.2	2.247	2.204	4.451	5.379	+0.928
3. High phosphorus diet plus calcium gluconate by mouth (10 gm. daily)	1	6	+70	4.5	2.605	2.611	5.216	5.870	+0.654
4. High phosphorus diet plus calcium lactate (3 gm. daily) and Drisdol (10 drops daily) by mouth	2	12	+31	4.0	2.417	2.058	4.475	4.703	+0.228
5. High phosphorus diet plus $CaCl_2$ intravenously (10 c.c., 10% solution t.i.d.)	2	12	+58	4.7	2.017	2.042	4.059	5.666	+1.607
6. High phosphorus diet plus dicalcium phosphate with viosterol (5 wafers daily)	3	18	+24	5.0	2.743	2.714	5.457	7.553	+2.096

which determine optimal absorption and utilization are maintained, such as low fat and neutral or slightly acid balance of the diet and proper phosphorus and vitamin D intake. We always give a high protein and high carbohydrate diet, and institute all other needs of good nutrition at the higher rate of metabolism. We use sex hormones when necessary.

We have advocated and used a high protein diet adequate in other respects in the treatment of hyperthyroidism for more than 20 years. Some investigators have thought that the osteoporosis of hyperthyroidism can be

TABLE 5

The Effect of Calcium Intake on the Calcium Metabolism of Several Cases of Hyperthyroidism

Type of Calcium Intake	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Calcium mg. %	Average Output per Three-Day Period			Average Intake per Three-Day Period gm.	Average Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. Low calcium	11	90	+48	11.0	0.784	2.016	2.800	1.423	−1.377
2. High calcium	5	81	+47	11.3	0.837	5.305	6.142	7.229	+1.087

prevented or even corrected by simply using a high protein diet. We have now studied five patients herewith included over 33 days on a high protein diet during low calcium and phosphorus feeding. These five patients were then studied over 66 days on a high protein diet but during high calcium and phosphorus intake. They retained calcium and phosphorus only when adequate amounts of these elements were added to the high protein diet.

When calcium loss has been severe, or has occurred over a long period of time, such as in patients with obvious osteoporosis, 3 gm. of calcium daily are a more adequate dose. We suggest that the high calcium diet be frequently supplemented by adequate intake of some form of dicalcium phosphate with viosterol, in order to restore these lost minerals. This product in our experience seemed to promote the retention of calcium and phosphorus 200 to 1000% over that of other forms of lime salt used.

Certain patients with impending thyroid crisis who did not respond to iodine therapy, or who escaped from iodine control subsequent to prolonged administration of iodine, were successfully and quickly prepared for surgery by use of adequate amounts of calcium, phosphorus and vitamin D, in addition to iodine and the usual general measures,[64, 66] without employment of the once widely advocated iodine vacation. Patients with severe acute spontaneous exacerbations of hyperthyroidism were more easily brought under control and more adequately and promptly prepared for surgery by use of this regimen,[66] together with the older principles which we have always

TABLE 6

The Effect of Phosphorus Intake on the Phosphorus Balance of Several Cases of Hyperthyroidism

Type of Phosphorus Intake	Number of Patients	Total Days of Investigation	Average B.M.R. %	Average Blood Phosphorus mg. %	Average Output per Three-Day Period			Average Intake per Three-Day Period gm.	Average Balance per Three-Day Period gm.
					Urine gm.	Feces gm.	Total gm.		
1. Low phosphorus	5	33	+69	4.8	2.453	1.270	3.722	2.738	−0.984
2. High phosphorus	5	66	+49	4.5	2.406	2.326	4.732	5.834	+1.103

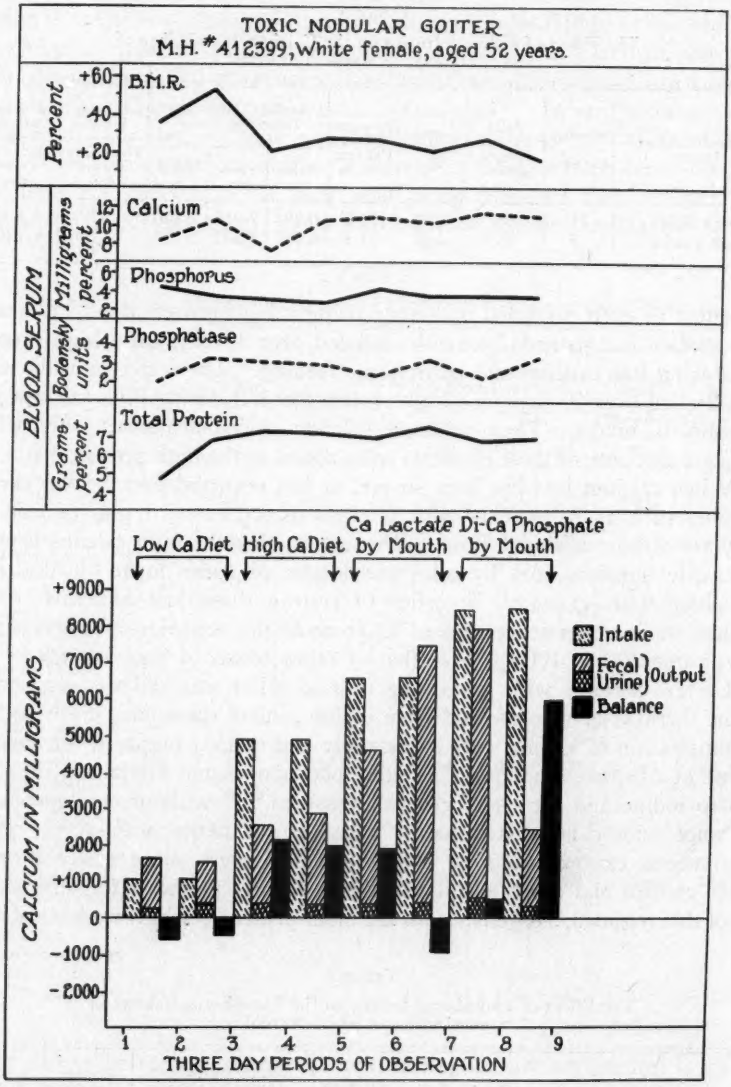


FIG. 14. Note the splendid retention of calcium with a high calcium and phosphorus diet, and particularly when supplemented by dicalcium phosphate with viosterol by mouth.

practiced, including judicious bed-rest, control of physical activity, freedom from emotional strain, adequate aeration, adequate sedation, a well balanced diet of high vitamin, high protein, high carbohydrate, and high caloric content, as well as adequate iodinization and treatment of existing com-

plications. Similar principles of treatment were carried out postoperatively. Recently, newer drugs such as the tranquilizers and reserpine have played an important part in this regimen. Long periods of preparation or of hospitalization have been frequently avoided by these methods. In most severe cases of hyperthyroidism where antithyroid drug therapy failed due to ad-

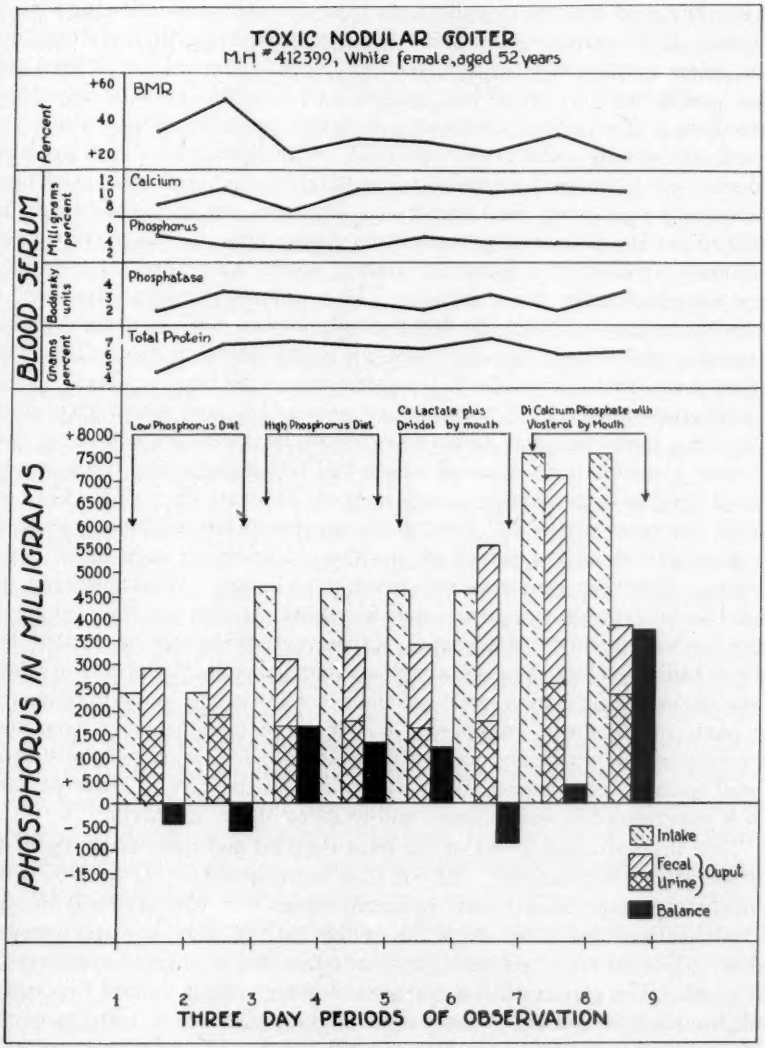


FIG. 15. There was similar great retention of phosphorus when a high calcium and phosphorus diet was given, supplemented by wafers of dicalcium phosphate with viosterol.

verse reactions, inadequate use of drug or drug insensitivity, our methods of preoperative and postoperative therapy proved valuable, so that operation was done early.

Utilizing all these methods,[66] we now do most thyroidectomies for hyperthyroidism safely after eight to 10 days of preparation. We have had no deaths in 1,453 thyroidectomies over 14 years done in seven different hospitals. The early and late complications have also decreased following thyroid surgery. For instance, in our last 100 patients requiring thyroidectomy for toxic goiter up to two years ago, who have been observed for at least two years postoperatively, there has occurred no thyroid crisis or hypoparathyroidism. One patient developed a recurrent hyperthyroidism which was treated successfully with propylthiouracil. One developed slight hypothyroidism. No permanent recurrent nerve paralysis occurred. One sustained a temporary right vocal cord paralysis. This was due to paresis following gentle stretching of the right recurrent laryngeal nerve. This nerve coursed abnormally anterior to a recurrent solitary nodule subsequent to thyroidectomy elsewhere eight years earlier. The vocal cord function returned to normal in 46 days. Of the last 100 thyroidectomies, 37% were for nontoxic uninodular goiter and 21% for nontoxic multinodular goiter. Three per cent were for thyroiditis and 4% for carcinoma of the thyroid gland. Toxic nodular goiter totaled 21%, toxic diffuse goiter 13%, and mixed toxic goiter 1%. It is significant that 35% of our thyroidectomies are still being done for toxic goiter patients, some of whom had had unsuccessful trials at antithyroid drug and radioiodine as sole methods of treatment. Ninety-six per cent of our most recent 200 toxic goiter patients were adequately prepared for surgery without the use of the antithyroid drugs or radioactive iodine therapy. Four per cent required antithyroid drugs. We considered less than 1% inadvisable to operate, and for these patients we resorted to the other modern methods of therapy. Hyperthyroidism can be treated best only by utilizing all of the general and specific principles,[66] and this of course demands individualization and judicious combinations and alterations of the plans of treatment employed. Under these circumstances, competent surgery presents practically none of the potentials for tragedy if the surgeon is well trained, experienced and conscientious in the care of these patients, and is experienced in the anatomy and technics of the operation.

True thyroid crisis is one of the most dreaded and most alarming of the postoperative complications. At one time it accounted for 25 to 50% of the immediate postoperative deaths in many clinics. It still occurred in spite of iodinization, and often occurred in the patient who was refractory to iodine. The causes of refractoriness to iodine and of thyroid crisis remain unknown. The glands of these patients, however, often showed hyperplasia with thinning or absence of the colloid. These phenomena were associated with lack of involution of the hyperplastic gland. Most evidence points to the fact that iodine therapy produces remission of thyrotoxicosis principally by increasing colloid storage of active organic iodine compounds. This

is well shown by histologic examination, which reveals marked colloid involution of the gland, as well as by iodine analysis,[62, 63] by radioiodine autography,[46] and by radioiodine fractionation of the excised gland which shows a high content of organic as well as inorganic iodine in the colloid.[47, 69]

In 1920 Kottmann [43] showed that calcium increased the viscosity of the colloid in the thyroid gland. Cameron [14] pointed out that, of tissues other than bone, the thyroid gland has the highest concentration of calcium. Abelin [1] revealed that calcium has an inhibitory action on thyroxine. The studies of Hellwig [30] did not support the view that calcium produces its effect through neutralization of thyroxine. He demonstrated experimentally [31, 32] that the hyperplastic thyroid stored much colloid during simultaneous high calcium and high iodine feeding. Thompson [79, 80] showed in 1933 and 1936 that in rats on diets containing the same amount of iodine, the blood iodine level was comparatively lower in the groups receiving additional calcium than in controls. In 1934 Klein [39] was able to show that a high calcium diet promoted a greater storage of colloid during iodine therapy than that produced by iodine therapy alone. It is this augmentation of the storage of colloid which may explain the therapeutic action of calcium in reversing an iodine-resistant state to that of iodine remission and in preventing thyroid crisis. De Robertis and Nowinski [20, 21] concluded from their experiments that the therapeutic action of iodine on the thyroid gland is due to the inhibition of the proteolytic enzyme system. It is possible that calcium may enhance this iodine effect.

We have given all our patients with hyperthyroidism a high calcium, high phosphorus and high vitamin diet for years, fortified by added amounts of calcium, phosphorus and multivitamins when necessary. We have been impressed with the much smoother postoperative course. Of 1,453 thyroidectomies, none developed thyroid crisis postoperatively, even before the advent of antithyroid drugs or radioiodine therapy. The senior author has not had one personal case of postoperative thyroid crisis over a period of 17 years of doing thyroidectomies. With this regimen and other sound principles of preoperative and postoperative medical and metabolic management, including iodinization, the iodine-resistant patients with impending crisis, particularly following the prolonged administration of iodine, were brought to remission. Similarly, patients with severe acute spontaneous exacerbations of hyperthyroidism were more easily brought under control and more adequately and promptly prepared for surgery. We know that when therapeutic doses of iodine are given to people with toxic goiter it does result in hyperinvolution of the hyperplastic gland, and that its beneficial effects are almost directly related to the extent of the hyperinvolution. The exact mechanisms by which iodine accomplishes this are still not completely understood. From experimental evidence set forth above by Kottmann, Abelin, Hellwig, Thompson and Klein, we have reasons to believe that proper calcium therapy enhances this therapeutic effect of iodine by aug-

menting further storage of iodine-rich colloid in the hyperplastic gland, which explains its ability to reverse an iodine-resistant state to iodine remission. The recent work of Taylor,[78] presented before the American Goiter Association in 1954, which shows that a high calcium diet increases the uptake of radioiodine by the hyperplastic gland of his animals receiving a high iodine diet, seems further to substantiate our theory.

We still emphasize that, along with any method of treatment of toxic goiter, it is simple to give adequate calcium, phosphorus and vitamin D for at least as long as hyperthyroidism persists to prevent the grave depletion of these elements which inevitably will occur in the hyperthyroid patient who is inadequately treated.

Summary and Conclusions

1. Eleven hyperthyroid patients maintained on a relatively low intake of calcium, averaging 474 mg. per day over a total period of 90 days, showed an average loss of 459 mg. per day. When five of these patients were further investigated on an adequate intake of calcium from different sources, averaging 2,410 mg. per day over a total period of 81 days, remarkable retention of calcium occurred which resulted in a positive balance of 362 mg. per day. The state of the phosphorus balance showed similar spectacular and beneficial changes. Retention occurred whether calcium and phosphorus were fed or administered parenterally.

2. We supplemented the high calcium and high phosphorus diets with four of the most common types of calcium salt used in therapy. They were all effective in maintaining retention of calcium and phosphorus. However, three of the 11 patients in our series received added amounts of phosphorus and vitamin D in the form of dicalcium phosphate with viosterol besides the added amounts of calcium. This product appeared to be superior to all calcium salts used. It seemed to promote increased retention of calcium and phosphorus of 200 to 1,000% over that attained in patients receiving only added calcium or calcium and vitamin D in palatable doses.

3. When it is realized that frequently the average American diet is still barely sufficient to supply the normal adult requirements, then it is easily understandable that, with the greatly altered metabolism of these two elements in hyperthyroidism, grave depletion exists which should indicate urgent need for the application of prophylactic and remedial measures. Ordinarily, hyperthyroid patients require about 2 gm. of calcium given daily to maintain them in calcium retention. This is at least twice the optimal calcium requirement for normal adults. When calcium loss has been severe, or has occurred over a long period of time, a more adequate dose is 3 gm. Phosphorus requirements are similarly greatly increased.

4. In the presence of insufficient calcium and phosphorus intake, hyperthyroidism often produces definite osteoporosis, which may even be detected roentgenologically. Severe cases of osteoporosis may lead to osteomalacia

and spontaneous fractures. Gross deformities and dwarfism may result. Practically, these complications of hyperthyroidism can be treated best by prevention, with feeding of adequate calcium, phosphorus and vitamin D, and early diagnosis and treatment of the hyperthyroidism. In late stages orthopedic measures may be necessary.

5. Muscular, joint and bone pains are often associated. These can frequently be best controlled by calcium, phosphorus and vitamin D therapy.

6. Calcium, phosphorus and vitamin therapy produce no demonstrable deleterious effects in hyperthyroidism provided the renal function is normal.

7. All hyperthyroid patients who for some reason do not come to surgery early should be treated with a high mineral-vitamin diet, fortified by additional amounts of calcium, phosphorus and vitamin D. Adequate amounts of calcium, phosphorus and vitamin D should be given not only in the preoperative and postoperative care of the patient, but also to the inoperable case, to the patient who refuses operation, or to the patient who is being treated conservatively by older medical methods, by antithyroid drugs, by radioiodine, by x-ray, or by a combination of these methods of therapy, for the reason that in the latter forms of treatment there is frequently a delay in obtaining the desired level of antimetabolic effect, and at times this level is never attained. We advocate therapy under these conditions to maintain a positive calcium and phosphorus balance and thus prevent the grave depletion of these elements which inevitably will occur in the hyperthyroid patient who is inadequately treated.

8. There are so many factors that have played such an important part in the decreased morbidity and mortality of hyperthyroidism that no one factor can be considered solely responsible. It must be emphasized that at present there is still no definite, dependable single method by which all hyperthyroidism can be treated. Until our methods are improved, the treatment of hyperthyroidism will be furthered by utilizing all of the known general and specific principles. This of course demands individualization and judicious combinations and alterations of the plans of treatment employed by both the physician and the surgeon.

Summario in Interlingua

Hyperthyroidismo, occurrente sub le conditiones del typic dieta american, es characterisate per un balancia negative de calcium e phosphoro. In le curso del tempore, grados significative de osteoporosis pote facer se clinicamente evidente.

Le autores ha monstrate in 11 casos de hyperthyroidismo, studiate metabolicamente, que le balancia negative de calcium e de phosphoro (que es presente sub le conditiones de un basse ingestion de calcium e de phosphoro) pote prestemente esser cambiate in un balancia positive per medio de un dieta e un medication que augmenta le ingestion de calcium e de phosphoro e in certe casos per medio del administration de vitamina D.

Omne patientes hyperthyroide le quales, pro un ration o un altere, non es operate in bon tempore debe reciper un tractamento special, consistente de un dieta adequate que es ric in proteina, carbohydratos, minerales, e vitaminas e que es fortificate per

supplementos de calcium e de phosphoro e, si necessari, etiam de vitamina D. Quantitates adequate de calcium, phosphoro, e vitamina D debe esser administrate non solmente como parte del tractamento pre- e postoperatori del patientes; illos debe etiam esser administrate in casos inoperabile, a patientes qui refusa le intervention chirurgic, e a patientes qui es tractate conservatorimente per altere methodos medical, per drogas antithyroide, per iodo radioactive, per radios X, o per un combination de iste methodos therapeutic, proque in omne iste ultime formas de tractamento il es un occurrentia frequente que le desirate nivello del effecto antimetabolic es retardate, e in certe casos iste nivello es nunquam effectuate. Sub tal conditiones nos recommenda un therapia capace a mantener un balancia positive de calcium e de phosphoro, con le objectivo de prevenir le grave depletion del duo mentionate elementos, proque iste depletion occurre inevitabilemente in le patiente hyperthyroide qui recipe un tractamento inadequate.

Multe factores ha habite un importante parte in le reduction del morbiditate e mortalitate per hyperthyroidismo, e nulle de illos pote esser considerate como individualmente responsabile pro ille effecto. Il debe esser signalate que il existe non ancora un definite e efficace methodo individual per que omne casos de hyperthyroidismo pote esser tractate. Usque nostre methodos es meliorate, le tractamento de hyperthyroidismo va profitar del utilisation de omne le cognoscite principios general e specific. Isto, evidentemente, require alte grados de individualisation e combinationes judiciose, con alterationes del planos therapeutic initiate per le medico e per le chirurgo.

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CLINICAL STAFF CONFERENCE

FACTITIOUS DISEASES: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Moderator: JOSEPH J. BUNIM, M.D. *Discussants:* DANIEL D. FEDERMAN, M.D., ROGER L. BLACK, M.D., RUDI SCHMID, M.D., LEON SOKOLOFF, M.D., and JAY SHURLEY, M.D., *Bethesda, Maryland*

DR. JOSEPH J. BUNIM: Since the Clinical Center opened in July 1953 we have protested that this is not a diagnostic center, nor is it an institution devoted primarily to the care of patients. Our primary responsibility is to design and conduct clinical research studies. Before we embark on investigative studies, however, it is most important that we arrive at an unequivocal diagnosis independently in each case referred to the Clinical Center. We have found that a surprising number of patients have had diseases that had not been recognized before admission. How closely the presumptive diagnosis simulated the "real thing" and how subtly in some cases the patient was able to duplicate and mimic the symptoms and, indeed, the signs of the condition supposedly present on admission, will become evident as the cases that follow are presented.

The first case is that of a young male patient with the diagnosis of islet cell tumor who was admitted to the Clinical Center by Dr. Federman.

DR. DANIEL D. FEDERMAN: This patient was a 22 year old male who was referred to the hospital because of persistent episodes of hypoglycemia. His medical history revealed that he had had diabetes when he was nine years old. At that time he developed polyuria, polydipsia, polyphagia and weight loss, and was hospitalized. Diagnosis was made promptly, coma was averted, and he was started on insulin, a mixture of protamine and crystalline. The dosage was gradually increased to about 9 units daily, and on this he was regulated fairly well. He had no instance of coma, or frank acidosis, although he had very frequent glycosuria and occasional hypoglycemic reactions. These were often correlated with more exercise than usual, and almost always were recognized early. They occurred during the day and were usually aborted by some carbohydrate taken orally.

About two years before he was admitted to the Clinical Center he began to have severe insulin reactions. These differed from his previous reactions in that they occurred frequently at night, were unrelated to exercise, and apparently came without warning. As these reactions increased in frequency and severity his insulin dosage was gradually reduced over a nine-month period. At the end of that time, a year before he was admitted here, his insulin was discontinued, yet he continued to have reactions. Many of these were quite severe, resulting in unconsciousness, oc-

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casional convulsions requiring intravenous glucose, and several hospitalizations at various times for relief. During one reaction he was found unconscious, slumped over the wheel of his automobile at about 6 a.m. He had apparently been there at least six hours.

A year before he was admitted here he was hospitalized elsewhere for study. His general physical examination and laboratory studies at that time were within normal limits except for inconstant glycosuria and hyperglycemia. Liver function tests, including cephalin flocculation tests, blood cholesterol levels and bromsulfalein retention, were all normal. Several studies of urinary excretion of steroids were within normal limits. It was therefore concluded that this patient had no adrenal or liver disease.

Two tests to demonstrate the pattern of his hyperinsulinism were carried out. In the first, a 24-hour fast was instituted. The glucose concentration of the blood at the beginning of the fast was 146 mg.%, and at the end of it was 10 mg.%. The patient was asymptomatic, although a bit tired. A few days later an oral glucose tolerance test was done. He was given 100 gm. of glucose within one hour, and after three hours the blood sugar had risen to abnormal levels, but at the end of seven hours it was well into the hypoglycemia range. He was irrational and required intravenous glucose for relief. He was discharged from the hospital, but was re-admitted a week later and an operation was performed. At laparotomy the pancreas was carefully explored from the head to the tail. No abnormality was found, but a subtotal pancreatectomy was done. Pathologic examination confirmed the surgeon's impression that the pancreas contained no adenoma.

After the operation the patient's diabetes became considerably worse. He required crystalline insulin several times daily, and gradually was shifted to long-acting insulin. About a month after this hospitalization, however, his hypoglycemic reactions recurred, and the same sequence evolved. His insulin dosage was gradually decreased. His parents were taught to give him subcutaneous epinephrine to correct episodes of hypoglycemia which occurred at home and frequently at night. About a month and a half after operation he was started on prednisone. It is not clear what dosage he took, but it varied between 2½ and 15 mg. daily, and there seemed to be some decrease in the frequency of his attacks. Insulin was withheld, however, and he continued to have glycosuria when he was not having hypoglycemic episodes. Prednisone was continued in varying dosage, and he was admitted to the Clinical Center about 10 months after it was started. The hypoglycemic reactions had varied in frequency. He probably had about two a week during most of that time. Perhaps a third of all the reactions during the 10 months prior to admission required some kind of medication or intravenous glucose, and many were accompanied by convulsions.

On the day the patient was admitted here, physical examination and routine laboratory studies were normal. While he was being examined in another room his own room was searched and a box containing an insulin syringe, needle, and a bottle of U-80 insulin was found. We substituted saline solution for insulin to prevent him from giving himself more insulin while in the hospital. That evening he was confronted with the evidence we uncovered, in as gentle a way as we could manage. He blurted out with apparent relief that he had been giving himself insulin all this time. We could not determine the dosage exactly because he seemed confused about unitage and syringes. As nearly as we could estimate, he had been giving himself about 80 or 100 units of a mixture of NPH and crystalline, in addition to his daily insulin dosage, during the periods he was given insulin, and at random intervals after prescribed insulin had been discontinued. During most of this time, afternoon tests for glycosuria were positive but morning tests were usually negative.

We asked him about this behavior in a rather superficial way, since his prolonged care would not be undertaken here. His immediate answer was that he was disappointed in the nature of the care of his diabetes, that treatment had not been more zealously administered. As nearly as we could determine, the recommendations of his physicians were sound and the patient had received optimal care. Unfortunately, the patient was discouraged by the inevitability of the complications of diabetes and by the inexorable progression of the disease. Because of this, he said, he felt he needed to take the treatment of it into his own hands. We asked him why he had let this situation develop to the point of requiring an operation. He told us that he had had occasional episodes of epigastric pain not well correlated with food or exertion or hunger, and not associated with abnormal physical or radiologic signs. He had been disappointed in the lack of a definite diagnosis, and thought that if an operation were done, even though not aimed at this symptom, something might be found which, if corrected, would abolish his abdominal pain.

He was in the Clinical Center a little more than a week and was regulated on 40 units of NPH and 12 units of crystalline insulin, given in one syringe in the morning. He had no reactions while he was here.

DR. JOSEPH J. BUNIM: This reminds me of a patient who was admitted to our Institute shortly after the Clinical Center opened. He was referred from Chicago with the diagnosis of islet cell tumor. He was a young man in his twenties, with a typical syndrome, and all the tests indicated islet cell tumor. He had been operated upon in Chicago and about two thirds of the pancreas had been removed. On very careful section, however, no tumor was found. In his case, as in the one just presented, a careful search was made of the room when the patient was taken out for x-ray. No evidence of self-administration of insulin was found, and it was decided that this was a bona fide case. Fortunately, on exploration of the head of the pancreas (which evidently had not been well mobilized at the previous operation), a small islet cell tumor was found and the patient was cured. It is important that a thorough search of the patient's possessions and room be made before attempting removal of an islet cell tumor.

The next case is one of especial interest to those concerned with rheumatic diseases, but it may be of some interest to others as well.

DR. ROGER L. BLACK: This patient was a 48 year old white female who was first admitted to the Clinical Center in March, 1957, with a 20-month history of polyarthritis. She had experienced an episode of hyperthyroidism which was treated surgically in 1945. Two years later she had pain in the finger joints for a brief period which had subsided spontaneously. The onset of the present illness dates from July 2, 1955, when she developed pain in the left shoulder following a period of rather strenuous activity. At first she thought it was bursitis, but the process spread to involve her right shoulder as well, with severe limitation of motion. She was hospitalized on July 26, 1955, at which time she was unable to lift either arm above shoulder level. She received Butazolidin and deep x-ray therapy, with little relief, and was later started on weekly injections of gold compound. Relief finally was obtained with local injections of hydrocortisone. Later her ankles and knees became painful and tender, and she again improved with intra-articular injections of hydrocortisone. The patient was discharged from the hospital in August, 1955, and later developed involvement of her elbows and both wrists. She was given ACTH in addition to gold compound and local hydrocortisone. Later, cortisone was administered orally in doses ranging from 100 to 400 mg., but this was discontinued in September, 1956.

During this period the patient's life was complicated by a series of unfortunate events. In November, 1955, her father died of heart disease. Her husband, who had had a mild myocardial infarction in 1948, was suffering left-sided weakness following a cerebral vascular accident. His illness required hospitalization during the spring of 1956, and the patient spent much of her time in the hospital helping to care for him.

In March, 1956, and again in June, biopsies of a persistent ulcer in the skin of her left ankle were performed. On June 20, 1956, her husband died. Shortly afterward she experienced a flare-up of her joint symptoms. She stated that her joint pains occurred at more frequent intervals following the death of her husband, usually every two or three days. In October, 1956, gold therapy, which had been discontinued in January of the same year, was reinstituted, but was again withdrawn because of an urticarial skin rash.

On November 2, 1956, the patient was admitted to the Johns Hopkins Hospital for observation, and was discharged December 15. A biopsy of the synovium of the left knee showed a foreign body reaction. While she was at the hospital ACTH and cortisone were discontinued, and the patient was treated with high doses of penicillin. At first, 3,000,000 units a day were given by injection, and then, beginning December 14, 12,000,000 units daily were given orally. This was continued through March, 1957, together with 1 gm. of Benemid daily. The patient continued to complain of intermittent pain in most of her joints. Pain and tenderness were most marked in the wrists and left knee. During the latter part of February, 1957, she was given buffered aspirin in daily dosage of 4.8 gm.

Physical examination on admission to the Clinical Center revealed a rather undernourished white female in no acute distress. Positive physical findings included an apical systolic cardiac murmur, several small lymph nodes in each groin, and swelling and tenderness of the soft tissue of the wrists and left knee. The affected areas on the wrists were restricted to the flexor surface and resembled abscesses. Small needle marks were present near each of these red, tender, fluctuant areas. The left knee showed generalized swelling of the suprapatellar bursa with apparent synovial thickening. The patient's temperature on admission was 38.4° C. Laboratory studies revealed a hematocrit of 31%, a white count of 3,900, with a normal differential, a sedimentation rate of 51 mm. (Westergren), and the presence of C-reactive protein (4+) in the serum. The serum uric acid concentration was 1.5 mg.%. Serum proteins showed an A/G reversal. X-ray of the joints showed soft tissue swelling involving the distal and proximal interphalangeal joints of both hands. Soon after admission the patient was seen by Professor Jonas H. Kellgren, who made the diagnosis of factitious arthritis. One day after admission her temperature was normal, but on the fourth hospital day the temperature rose to 38.2° C. The patient complained of exquisite pain and swelling of the left elbow.

On careful examination of this area three small puncture marks were observed near the medial condyle of the left humerus. Blood cultures were obtained, and penicillin and streptomycin were administered. She was questioned about the small needle marks near her left elbow, and her first explanation was that she had scratched her arm on some pins in her dress. Later she said that before leaving home she had given herself an injection of Demerol, but in an attempt to inject it into her shoulder she missed and caught the needle in her elbow.

A search of the patient's hospital room and personal property revealed the presence of three hypodermic syringes, five hypodermic needles, two small bottles of liquid and several small bottles of tablets. These were returned to the room, and the next day the patient surrendered this material on request. She stated that one of the bottles of liquid was Demerol, the tablets were Demerol, and the other bottle of liquid was ACTH. The case was discussed with Dr. Sokoloff, who had studied the

biopsies previously taken. He suggested that the material in the biopsied areas contained exogenous mineral matter, probably talcum. The psychiatric aspects of the case were then discussed with Dr. Shurley, since it seemed fairly certain that the patient was introducing some substance into her joints in order to cause an inflammatory reaction.

It was decided that the patient should be confronted directly with the clinicians' opinions. When this was done, she requested immediate discharge. A search of her suitcase prior to discharge revealed a small envelope of surgeon's talc and a small perfume vial containing a liquid suspension of whitish flocculent material. The patient promptly left the hospital against medical advice, but a week later she telephoned us to say that we were correct in believing that she was injecting her joints. She said that, although previously she had required a fair amount of Demerol in order to be comfortable, she was making a sincere attempt to discontinue the use of this drug. She requested permission to come back to the Clinical Center to obtain psychiatric help. We suggested that this help could best be obtained through her referring physician.

DR. JOSEPH J. BUNIM: The next patient also presented an interesting challenge in diagnosis and was thoroughly studied by Dr. Schmid, who will present the case.

DR. RUDI SCHMID: The patient was a 33 year old white housewife who was admitted here for acute intermittent porphyria. The history was somewhat unreliable, and changed a great deal as different interrogators took it.

At age six the patient had first experienced intermittent cramping pains in the lower extremities. We were unable to get more details regarding the nature of this pain, but apparently it has been intermittently present from age six to the time of admission. At age 12 she was found to have anemia which was severe enough to require transfusions. She was given several medications to increase her hemoglobin level, but they were without lasting benefit and she continued to suffer from anemia throughout her teens, requiring occasional transfusions.

At age 14 she first experienced episodes of sudden blindness, usually associated with nausea and vomiting. These lasted from one to four hours and were frequently followed by severe headaches. They had occurred as frequently as once or twice a month, but after age 20 the frequency gradually decreased. Around that time she first noticed "photosensitivity." What she meant was that she burned easily upon exposure to the sun. At age 22 there developed progressive paresthesia and weakness in all four extremities, especially in the legs, resulting in inability to walk. At the same time, her urine was frequently noted to be of either dark or cherry-red color. Excretion of pigmented urine was usually associated with abdominal pain and muscle cramps.

At age 30 an appendectomy was performed, apparently for severe and recurrent abdominal pain. The operation was followed by complete paralysis of the lower extremities and blindness, which lasted for seven months and then gradually improved. She was bedridden for almost a year, and later was in a wheelchair, until she gradually began to walk again.

At age 32 the patient was found to have a hemoglobin of 4 gm., and was immediately hospitalized and given transfusions and prednisone. She improved somewhat and was back on her feet when, at the age of 33, she had a relapse with severe paralysis and paresthesia and was confined to bed. She was admitted to the Clinical Center with the diagnosis of acute intermittent porphyria.

On review of the history of this patient, a number of features were difficult to reconcile with the diagnosis of acute hepatic porphyria. Except for the episode at

age 30, which led to the appendectomy, intermittent abdominal pain was not prominent among her various complaints. Although the exact nature of her alleged "photosensitivity" was never clearly defined, it should be remembered that photodermatitis and epidermolysis bullosa are not observed in hepatic porphyria of the intermittent acute type. Furthermore, hepatic porphyria is usually not associated with anemia, and the presence of a hemoglobin concentration of 4 gm.% must have another explanation. I have never heard of recurrent episodes of transient blindness associated with porphyria, and I know of only a few cases where retrobulbar neuritis led to permanent visual impairment. Finally, in intermittent acute porphyria, the urine is usually of normal color when passed, but darkens on standing in daylight. As a rule, the color of light-exposed urine is not red but brown, resulting supposedly from the oxidation of porphobilinogen to the ill-defined pigment porphobilin.

On admission some additional information was obtained. The patient was married and had one child, but apparently had made a very poor marital adjustment and had had a great many emotional problems. She was unwilling to accept her husband, her child, or her duties as a housewife. She had been trained as a medical technician, and had been employed in a small private hospital in the Midwest. Apparently she had been somewhat of a factotum in this hospital, and knew her way around the laboratory, diet kitchen, pharmacy and staff offices. She had had free access to the drug room, and had received courtesy treatment from the attending staff whenever necessary. Among other things, she had been taking steroids, Dramamine, chlorpromazine, quinine, barbiturates, vitamin preparations and 2 gr. of thyroid daily.

On admission, the patient was quite emaciated, bedridden, and unable to stand because of severe weakness in the extremities. Muscle atrophy or fasciculations were not detected. The tendon reflexes were hyperactive but equal. Pathologic reflexes were not demonstrable. Examinations of the sensory system performed by several members of the National Institute of Neurological Diseases and Blindness failed to reveal a persistent pattern. Ophthalmoplegia or other eye signs were not observed. The blood pressure was 112/60 mm. of Hg, and the heart rate was rapid and regular.

The hemoglobin was 11.4 gm.%; white blood cell count, differential and blood sugar were normal; cholesterol, 172 mg.%. Conventional liver function tests were within normal limits. The spinal fluid was under normal pressure, cell free, and chemically normal.

The lack of positive findings on physical and laboratory examinations suggested the possibility that the patient was suffering from a bizarre functional disorder. Some of the features, however, could not be explained on this basis—for instance, the persistent sinus tachycardia, which increased steadily after admission. And there was this oddly colored urine.

On admission the urine exhibited a deep red color resembling cherry wine, and on spectroscopic examination a single broad absorption band with a maximum around 550 mμ was found. The spectroscopic findings were unlike those seen in porphyria, but on gross inspection the color of the urine was compatible with massive porphyrinuria, such as is seen in congenital erythropoietic porphyria. On exposure to ultraviolet light, however, no red fluorescence was demonstrable. If the color of this urine had been due to the presence of porphyrins one would have observed a most impressive red fluorescence. These findings clearly indicated that we were not dealing with porphyrins.

Our attention was then called to the possibility that the patient might be ingesting something which would cause the excretion of red urine. In an attempt to get some information we searched her room and found about one-half pound of a white powder which had not been delivered to the nursing staff, although the patient had been instructed to deposit all medications brought from home at the nursing station.

We removed a small aliquot of this white powder and left the remainder in the drawer. The white powder was given to a rat by stomach tube, and the animal was put into a metabolism cage to permit collection of the expected red urine, but we did not get any urine. All we got was a grossly bloody diarrhea, because the powder was Epsom salt!

So we had to try again. We now paid a little more attention to the urinary pigments. On the day of admission the urine had been of a deep red color, but on the next day the urine was yellow, and there was not a trace of a red color. However, on addition of Ehrlich's aldehyde the urine assumed a beautiful red color, which seemed to suggest the presence of porphobilinogen. On spectroscopic examination, however, the sharp absorption band at 560 mμ and the weaker band at 525 mμ, so typical for the porphobilinogen-Ehrlich's aldehyde complex, were absent. Ultimately, it was discovered that it was not the Ehrlich's reagent which was responsible for the development of the red color but the HCl in which the Ehrlich's reagent was dissolved. When the urine was acidified the red color appeared; when alkalinized, the urine again turned yellow. The compound in the urine acted as an indicator, with a turning point around pH 7.

On the patient's third day in the hospital the amount of red color extracted in acidified urine was considerably less than on the day of admission, and on the fourth day it had almost completely disappeared. In discussions with the patient we were struck by the fact that she was familiar with Pyramidon, or antipyrine, although she had never heard of Miltown. (Pyramidon is a drug now used infrequently in this country because of the relatively high incidence of leukopenia associated with its use.)

Pyramidon is dimethylamino-antipyrine, and it is well known from earlier studies that this compound frequently produces red urine. The pigment responsible for the red color is rubazonic acid, a condensation product of two of the antipyrine rings. The compound is red in acid and yellow in alkaline solution. Attempts to isolate rubazonic acid from the urine in crystalline form were successful, and we obtained a lot of nice crystals—of course confirming our suspicion that the patient had been taking Pyramidon. When this was brought to her attention she admitted taking large amounts of this drug which, many years ago, she had obtained from one of her physicians. She had noticed that the compound resulted in the excretion of red urine which, in turn, seemed to create considerable interest among the attending staff. The patient made use of this trick whenever new evidence was needed to support her numerous and varied complaints.

Pyramidon explained many of the findings but not all. It did not, for instance, explain why the patient was gradually getting worse, or why she developed a fever of 105° F., or why she had a sinus tachycardia with a rate of 220 per minute. Furthermore, it did not explain why she was getting disoriented and delirious. She looked as if she had thyrotoxicosis, but she had no eye signs and no enlarged thyroid gland, although she was sweating and had a fine, rapid tremor. A radioactive iodine uptake was 12%, a value below the normal range. On the other hand, the protein-bound iodine was found to be 16 μg.%, which is much above normal. These two laboratory findings were suggestive of exogenous thyroid administration. After she had recovered from her acute attack, the patient admitted having taken a single dose of between 60 and 100 gr. of desiccated thyroid, an exceedingly large amount, which undoubtedly accounted for most of her manifestations.

But it did not account for all of her symptoms. In particular, it did not account for her history of severe anemia. At the time of our study her bone marrow, her serum iron level and her hemoglobin concentration were normal. We were at a loss to understand how, in the past, she could have had a hemoglobin of 4 gm.%. As it turned out, all of the hemoglobin determinations yielding low values had been done

by the patient herself, whereas those done by other technicians had yielded normal results.

DR. JOSEPH J. BUNIM: The next case was not so neatly solved before the patient was discharged as were the other cases discussed today, and I dare say that Scotland Yard would probably frown on the performance. Nevertheless, the case is instructive, and a solution did come after the patient was discharged. The case will be presented by Dr. Black.

DR. ROGER L. BLACK: This patient, like two of the previous three, was closely associated with a hospital at about the time of the onset of her illness. She was a 21 year old white female student-nurse who was admitted to the Clinical Center on August 25, 1954, with a three-year history of recurrent episodes of periarticular swelling and pain, accompanied occasionally by fever. She had been essentially well during her early life. In 1951 she had left home for the first time, to start her nursing training. Three months after leaving home, following an upper respiratory infection, she had developed aching sensations in both legs, with mild fever. She had been admitted to the hospital with a diagnosis of rheumatic fever, and had remained there for several months, with migratory joint pains and occasional joint swelling. The sedimentation rate had been slightly elevated (22 to 27 mm. per hour), but other laboratory studies had been within normal limits. After three months the symptoms had subsided, and the patient had been able to continue her training.

In September, 1952, January, 1953, and the summer of 1954, she had experienced brief episodes of migratory joint pain and swelling, involving especially her elbows and knees. During this period she had also had recurrent episodes of abdominal pain. In October, 1952, she had undergone a laparotomy because of abdominal pain, and a "chronically diseased" appendix had been removed. In February, 1954, another laparotomy was performed, and at that time an abscess was found along the left rectus sheath. During the postoperative course the patient had again developed migratory joint pain and had been treated with ACTH and hydrocortisone, in daily doses of 200 mg. There had been only slight improvement in her joint symptoms, and she had been referred to the National Institutes of Health for further study.

At the time of admission, physical examination showed no abnormalities of the head, eyes, ears, nose or throat. Blood pressure was elevated (160/110 mm. of Hg). The heart, however, was not enlarged. An apical systolic murmur (Grade 1) was audible. The lungs were clear, and no abnormalities of the abdomen were observed except for the surgical scars. Examination of the extremities showed hyperaesthesia over both knees and tenderness over both shoulders and hips. During the patient's hospital stay she experienced recurrent episodes of swelling and tenderness in many of her joints, each episode lasting for from one to five days.

On admission her sedimentation rate was 5 mm. and her white count 13,000, but the latter rapidly returned to normal levels of 5,000 to 9,000. Hematocrit was 42%; hemoglobin, 14 gm.%. The urine was normal, and the antistreptolysin titer was less than 50 units. Repeated L. E. cell tests were negative. Serum protein concentrations were within normal limits, as were the electrocardiogram and all x-rays of the joints.

The patient was first admitted to the National Heart Institute. No evidence could be found to substantiate the diagnosis of rheumatic fever. She did experience recurrent episodes of joint pain, swelling and tenderness, and on some of these occasions the temperature rose to 38.4° C. Her blood pressure was elevated for only two days, and then was normal for the remainder of her hospitalization.

The attacks of joint pain were usually monarticular. It was of interest that pain usually preceded objective signs of periarticular inflammation. Hydrocortisone,

which the patient was taking at the time of admission, was gradually reduced in dosage over a two-week period and was then discontinued. During the early part of her hospital stay she was treated with up to 900,000 units of penicillin daily, but after 10 days this was discontinued. During one attack of joint pain she received phenylbutazone, but as this produced no improvement it was also discontinued. For one period she received Benadryl, but during its administration she suffered another attack and this therapy was discontinued.

The diagnosis of palindromic rheumatism was considered likely, and the patient was transferred to the National Institute of Arthritis and Metabolic Diseases on October 18, 1954. She continued to have frequent exacerbations of joint pain and swelling, and during the episodes of pain doses of 400 to 600 mg. of Demerol daily were required to control her distress. In addition to this she occasionally received codeine for relief of pain. During the latter part of her hospital stay gold therapy was instituted, and she received a total of 450 mg. of Myochrysine. Biopsies were obtained from soft tissue around the inflamed joints, but when this material was cultured no organism was found. The histology will be discussed by Dr. Sokoloff.

It was of interest to the staff that on several occasions the patient was able to predict that an attack would develop before any objective evidence of joint disease was discernible. It was also noted that at times the patient's degree of pain seemed to exceed the degree expected on the basis of objective findings. Two significant observations were included in the nurses' notes. A nurse once went into the patient's room at 4 a.m. and found her left arm swollen and cyanotic, and a tourniquet tightly bound above the swollen area. The patient, apprised of this finding, claimed she didn't know how the tourniquet got there. Another time, also at 4 a.m., the nurse went into the room and the patient complained that there was a tingling sensation in her fingertips and about her mouth. The patient's fingertips were a deep blue, as was the skin about her mouth. The lights were on and the patient apparently had been writing letters. A bottle of blue ink was on the bedside stand. The nurse pointed out that the patient had probably accidentally dipped her fingers into the ink and then moved her finger around her mouth, but the patient denied this, and immediately asked for some cracked ice. The nurse went to the kitchen to get the ice, and when she returned the stains were gone.

Because of this peculiar behavior and the obvious need of the patient to seek attention from the physicians and nurses, consultation with a psychiatrist was arranged. Dr. Shurley saw this patient and will comment on his observations. The swollen tissue about the patient's elbow was not confined to the joint, but centered about it, and extended from the middle of the lower arm almost to the shoulder.

The patient was discharged on January 20, 1955, to return to the care of her local physician. It is of interest that in October, 1956, her physician reported to us that she had developed recurrent episodes of abdominal pain, with swelling and redness of the abdominal wall, associated with fever. He was impressed by the patient's emotional instability, and referred her to the University of North Carolina for psychotherapy. While undergoing this treatment she was employed as an office nurse for a local pediatrician, and during this period it was found that she was using Demerol. She was brought to court and sent to Lexington, Kentucky, for hospitalization and treatment for her narcotic addiction. Upon return to her home town she began to forge her physician's signature on prescriptions for Demerol. She was again arrested, and this time was referred to a state mental institution.

DR. JOSEPH J. BUNIM: We should comment on the patient's ability to predict the recurrent attacks of periarthritis and para-arthritis. Frequently patients with palindromic arthritis are able to predict about 24 hours in advance when their attacks will recur. (Incidentally, the nurses occasionally found this patient

in the medical library reading about lupus erythematosus, palindromic arthritis and allied conditions, so that she was certainly a well informed person.)

As to the first case of arthritis presented by Dr. Black, as was mentioned, a biopsy had been done at another hospital some time before the patient was admitted to the Clinical Center. Our intensive study of the sections revealed that the material in the biopsy was very likely talc. A biopsy was also done in the last case presented, and the findings in both cases will now be described by Dr. Sokoloff.

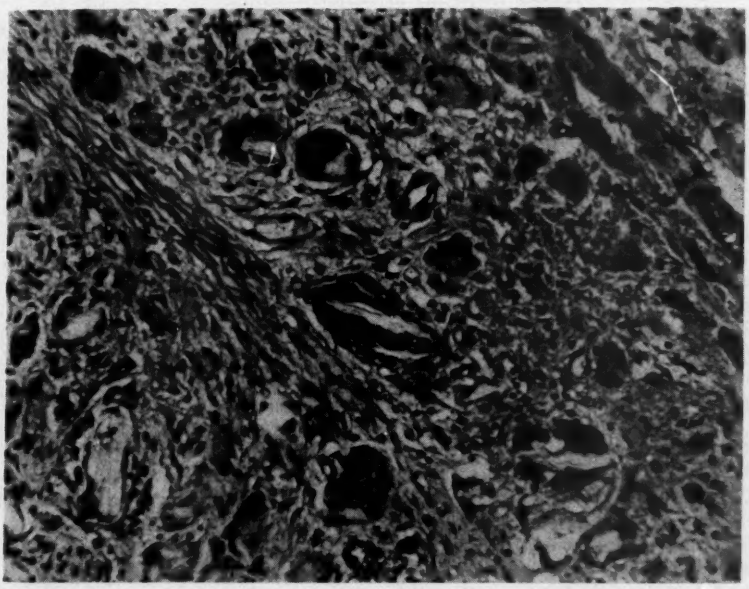

FIG. 1. Talcum powder granuloma in synovial tissue. Multinucleated foreign body giant cells contain irregularly shaped, pale crystalline material. Hematoxylin and eosin (225 ×).

DR. LEON SOKOLOFF: The tissue shown in figure 1 was obtained by biopsy of the knee joint when the patient was admitted to the Johns Hopkins Hospital, and the section was sent here for consultation. The lesion was a foreign body giant cell reaction located deep in the wall of the joint, rather than at the surface of the joint proper. There were nodular areas of infiltration by pleomorphic multinucleated giant cells that contained rather clear, blue-green appearing crystalline material. There was also some minor nonspecific chronic inflammatory reaction.

The problem was to establish the nature of the crystalline material. The paraffin block was sent to us through the courtesy of Dr. Kleinfelter, the Johns Hopkins Hospital. Sections were made and deparaffinized. The first procedure to characterize the crystals was to incinerate the slides in a muffle oven at 450° for a period of one-half hour. Nothing happened to the crystals, and for this reason it was assumed that they were probably of a mineral rather than of an organic nature. Furthermore, when concentrated sulfuric acid was placed on the sections no gas evolved, and this was presumptive evidence that we were not dealing with carbonate,

or oxalate, that might have become oxidized to carbonate during incineration. Also, several stains were made that were fairly characteristic histologically of certain inorganic materials. There was no iron by the ferricyanide method. Phosphate was ruled out with silver nitrate stain, as was picrate. There was no elastic tissue within the crystalline material. Thus we were dealing with a mineral material that did not contain calcium, iron, phosphate or carbonate. The crystals were highly anisotropic.

Pathologists are well aware of the occurrence of talcum powder granulomata. In the past, when talcum powder was used on surgeons' gloves prior to the use of soluble starch, this was seen frequently in the abdominal organs.

To confirm the possibility that this might be talcum powder, we consulted Lange's *Handbook* for its specific angle of polarization; there we found the refractive indices of crystals. We then set up a series of graded mixtures of alpha bromonaphthalene and mineral oil, which have widely differing refractive indices, and compared the extinction of the outline of the crystals in these different media to those of talcum powder. We found that the crystals in the tissues were well extinguished at the same refractive indices as those of talcum. We reported that this material appeared to be of exogenous origin, and mineral, and very likely was talcum powder. This report was questioned because it was felt that there was no way for the talc to have entered. It was pointed out that the patient had had one intra-articular injection of hydrocortisone into the knee joint prior to admission. It was conceivable that there was an excess of talcum powder on the gloves of the person who had made the injection, and that this could have been the route of access. Nevertheless, the patient had had a biopsy of an ankle lesion at the Medical College of Virginia some months previously. She had never had an injection of hydrocortisone into this joint, yet similar crystalline material was present there. This was a mystery which we had hoped could be resolved by admitting the patient to the Clinical Center.

There is nothing more to add about this case pathologically, except that we attempted to apply the method of refractive index determination to other crystalline materials that may occur in tissues. However, we had little success, because many of these substances have several different axes of polarization. For this reason, unless the actual crystallographic properties of the material are known, and unless the crystals are large enough and have rather linear margins, this method cannot be applied for general histologic diagnosis. We are fortunate that the talc happened to be the specific crystal involved in this case because two of its axes have the same refractive index.

In the sections from the other patient who had periarticular edema, adipose tissue had become necrotic in places and there was organization by nonspecific fibrous granulation tissue. The changes were simply those of edema of subcutaneous tissue with focal fat necrosis.

DR. JOSEPH J. BUNIM: When a clinician comes to the conclusion that he is dealing with a factitious disease, a number of questions at once concern him. How should he confront the patient, and what should he say? What might the patient's reaction be? How can he begin to uncover the underlying and perhaps unconscious conflict which gives rise to this apparent need to simulate organic disease? In such problems the clinician may get help by consulting the psychiatrist. We called upon Dr. Jay Shurley, and I am pleased that he is here to discuss these problems.

DR. JAY SHURLEY: The ingenuity of these patients was matched only by the ingenuity of the medical staff in discovering the true origin of the puzzling signs and symptoms. Although none of these patients was studied fully from

the psychiatric point of view, perhaps I can point out a few of the emotional factors which appear to be involved in this type of situation.

I did have an opportunity to see the second patient (self-induced talcum arthritis) briefly, and was struck by the incongruity of her statements and her behavior. She appeared to be sad, listless and indifferent to all about her, but stated that she enjoyed life, and was always considered tc be the "life of the party" in any group of which she was a member. She told me how she had spent 16 years of her life acting as full-time nurse to her ailing, partially paralyzed husband. Immediately upon his death three years before, she had fallen ill. To her physician she had said, "No one can imagine how difficult it is for a woman to battle the world alone." She wished that she had died when her husband did. On a later occasion she expressed some suicidal thoughts. But these depressive statements were often followed by an outburst of anger at the doctors who accused her of injuring herself. She said, "I wish I could leave here tonight, but I can't cut off my nose to spite my face. My husband was a big taxpayer, and I should stay here and get some benefits."

Behavior such as this is, of course, evidence of a serious emotional disorder. The picture presented is that of a person struggling with intense feelings of aggression and hostility. At times she turned these inward, and made herself the target—hence the self-inflicted injuries and the depressive feelings—but even in doing this she inflicted herself on others. At other times she turned her aggression outward—she expressed her hostility toward her physician and toward the Institute. This was possibly a life-saving maneuver, since she might otherwise have continued her self-destructive activity beyond the point of no return.

The psychiatric consultant saw the third patient twice but was unable to confirm the suspicion that her symptoms were self-induced. He felt that there was the rather bland, somewhat indifferent attitude toward the manifest severity of the illness which frequently characterizes the hysteric personality. He considered that this represented a psychologic defense, and recommended that it not be attacked lest the patient be driven to an even more serious emotional disturbance.

I should like to make some general comments about factitious diseases, and might take as my text an article by the dermatologist, S. E. W. Netherson, which appeared in the *Ohio State Medical Journal* in 1927. He wrote that many of these patients are subjected to repeated, extensive surgical procedures and may even suffer irreparable damage. Many cases are on record where a finger or even an arm has been amputated, or a laparotomy performed (as in the case of the first patient described by Dr. Federman). In addition to the economic loss involved in such cases, the inconvenience sustained by the innocent members of the family is little short of tragic. In these words Netherson put his finger on the important psychologic factors: ". . . the wish to suffer; the wish to cause others (particularly the family) distress, pain, and embarrassment." In varying quantity these factors are found in a wide range of conditions—from such factitious conditions as we have heard about today, to accident-proneness, to malingering, to self-mutilations, and even to suicide.

Why do these patients wish to suffer? Perhaps it will puzzle you if I say that they do so in pursuit of pleasure. But I mean pleasure in the sense of

personal security. There is evidence to support the belief that the security of these patients is threatened by an overwhelming sense of guilt, largely unconscious. Most often this guilt is in reaction to murderous hostility, also unconscious. Their self-punishment serves as atonement for this guilt, and thus, paradoxically, their physical insecurity serves to maintain their emotional security.

This leads me to one of the most important factors to be considered in the treatment of these patients. I can begin no better than by quoting Karl Menninger: "Physicians are accustomed to use their professional energies toward the end of alleviating suffering and healing disease. They are accordingly utterly confounded by such behavior as self-mutilation or self-induced simulated disease. Unable to detect any material advantage from the process, and unacquainted with unconscious gratifications, the physician is inclined to regard these acts as prima facie evidence of insanity. Where the self-mutilation appears to be capitalized by the patient for obvious secondary gain, the physician's attitude changes from bewilderment to indignation. Malingering, as he calls it, has puzzled and irritated clinicians for centuries. In malingering . . . there is the frank appearance of an aggressive purpose where in exploiting the secondary gains of the illness, the patient thwarts and deceives the physicians and others whose interests run counter to his necessity for continuing his illness. The patient thus finds himself in the predicament of fighting those who seek to relieve him. His aggressions are displaced from whatever or whoever provoked them onto the innocent physician—and because it is so unjustified, this aggression strongly stimulates the physician to retaliate."

What are we as physicians to do when caught in such a situation? Our anger and contempt may lead us to expose the fakery—but this does not help the patient; in some instances it may drive him to even greater excesses. Generally, these patients do require intensive psychiatric treatment. Though time is too short to go into any details, I might indicate the general direction the therapy may take. The psychiatrist asks himself if the feelings of pity, anger or exasperation he experiences may not be precisely those which the patient unwittingly is attempting to produce. He then attempts to discover, by indirect means, what, in the patient's previous experience, could account for such behavior toward others. Bringing these experiences to light may enable the patient to understand and control his irrational behavior. These are sick people, then, and as fit subjects for our investigative efforts as if they really did have islet cell tumors, or arthritis, or porphyria, or collagen disease.

In concluding, I should like to comment on some of the questions Dr. Bunim raised. I feel I handled my relationship with Dr. Black and his first patient somewhat clumsily. If I had it to do over again, I would advise Dr. Black to do two things as soon as he suspected that the disease was factitious: (1) lay the ground work for psychiatric consultation, and (2) avoid any procedure which might expose the patient. We must recognize that this behavior constitutes a necessary psychologic defense. If it is stripped away prematurely, at best the patient may leave the hospital as this one did; at worst, he may be precipitated into a frank mental illness, or even driven to suicide. These are psychologic illnesses, and rather serious ones at that. I believe the psychiatrist should be consulted in every case.

Summario in Interlingua

Es presentate quatro casos de morbo facticie que esseva studiate al Centro Clinic. Le diagnoses al tempore del hospitalisation esseva (1) tumor de cellulas insular del pancreas, (2) arthritis rheumatoide, (3) porphyria, e (4) febre rheumatic con polyarthritis. In omne iste casos il esseva constatate que le symptomas e anormal signos physic esseva auto-inducite. Le factores psychodynamic que es responsabile pro le comportamento de tal patientes es discutite per un psychiatro membro del personal. Es discutite le problemas con que le medico se trova confrontate in iste typo de situation.

CASE REPORTS

THE SYSTEMIC MANIFESTATIONS OF SJÖGREN'S SYNDROME: REPORT OF GLANDULAR FUNCTION WITH HISTOLOGIC, BACTERIAL AND VIRAL STUDIES *

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IN 1933 Henrik Sjögren [1] amplified Gougerot's original description [2] of a syndrome consisting of dryness of the mucous membranes and the eyes, with parotid glandular enlargement in menopausal women. Since then several excellent reviews [3, 4, 5] have emphasized that the disease is of a diverse nature, with such manifestations as polyarthritis, dryness of the vulva and vagina, diminished perspiration, Raynaud's phenomena, scleroderma, hypochromic anemia, alopecia, achylia gastrica and an altered glucose tolerance.

Infrequent attempts [6, 7, 8] have been made to study the pathogenesis of this condition by noting histopathologic changes occurring in accessible organs. The following report is an evaluation of the systemic nature of Sjögren's syndrome by some functional and histologic studies made in a patient with this disorder. The case is of further interest in that it occurred in a young male, rather than the usual postmenopausal female.

CASE REPORT

A 36 year old white male carpenter was admitted to the West Haven Veterans Administration Hospital on May 6, 1954, with the chief complaints of sore eyes, dry mouth, nasal stuffiness and bilateral facial swelling of three years' duration. Arthralgia of the large joints had been present for about five years prior to the admitting complaints, and on one occasion redness and tenderness of the right wrist had been present. The patient had been seen by several physicians, who had suggested the diagnoses of "adult mumps" and "Boeck's sarcoid." He had been treated with cortisone for about three months, with good relief of symptoms for one year. Thereafter, all complaints had recurred, and his arthralgia had become severe enough to require reinstitution of cortisone therapy. He was admitted at this time (December, 1953) to the New Haven Hospital, where hepatomegaly and hypertension of 160/120 mm. of Hg were found. Laboratory studies disclosed eosinophilia of 8%; nonprotein nitrogen, 50 mg.%; total proteins, 9.09 gm.% (albumin, 2.83 gm.%, and

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globulin, 6.26 gm.%; calcium, 10.59 gm.%; phosphorus, 5.63 gm.%). The discharge diagnosis was "sarcoidosis."

Past history was noncontributory. Review of systems disclosed a history of weight loss of 15 pounds in three years, and the appearance of transient hyperesthesias over various areas of the body so that even the mildest trauma would result in intense pain.

Physical examination revealed a well nourished, well developed male with a "chipmunk-like" facies (figure 1), who did not appear to be ill. Temperature was 98.6° F.; pulse, 76; blood pressure, 150/100 mm. of Hg. The parotid and submaxillary glands were diffusely and symmetrically enlarged, very firm and nontender. A 1 cm. indurated lymph node was palpable immediately posterior to the right sub-

FIG. 1. Pretreatment and post-treatment views of patient. The "chipmunk-like" facies illustrated on the left is due to marked parotid and submaxillary gland enlargement. The patient's salivary glandular enlargement (right) regressed to a near-normal state approximately two weeks after initiation of ACTH therapy.

maxillary gland. The conjunctivae and sclerae were markedly inflamed. The lacrimal glands were not enlarged; there was no moisture in the conjunctival sacs. The nasal turbinates were swollen, inflamed and very dry. Although the orifices of the salivary ducts appeared to be normal, no fluid could be expressed from the ducts. The liver was felt two fingerbreadths below the right costal margin and was soft and nontender. The spleen was palpated one fingerbreadth below the left costal margin. A 1.5 cm. soft, nontender, movable axillary node was present in each axilla.

Laboratory Data: Routine data on admission: Urinalysis: specific gravity, 1.010; albumin, 2 plus; sugar, negative; microscopic: 4 to 6 leukocytes/HPF. White blood cell count, 5,650, with 39% neutrophils, 42% lymphocytes, 9% monocytes, 6% eosinophils and 4% basophils. Hemoglobin, 15 gm.; hematocrit, 48. Sedimentation rate,

6 mm./hr. (Wintrobe method). A repeat white blood cell count: 6,000, with 35% neutrophils, 4% nonsegmented neutrophils, 46% lymphocytes, 4% monocytes and 11% eosinophils. VDRL test for syphilis was negative.

Hepatic Functions: Bromsulfalein, 5.9% dye retained at the end of 45 minutes (5 mg./Kg.); repeat bromsulfalein, 0.4%; alkaline phosphatase, 3.15 Bodansky units; total cholesterol, 229 mg.%; urinary urobilinogen, 0.09 unit; total serum bilirubin, 0.1 mg.%; thymol turbidity, 5.3 units.

Renal Functions (11-24-54): Urinary protein excretion, (biuret method): 0.24 mg./min. (maximum, 100 mg./daily, within normal range); nonprotein nitrogen, 54 mg.%; urea, 32 mg.%; repeat nonprotein nitrogen, 54 mg.%; Sulkowitch's test, negative; urine concentration test, maximal concentration 1.010; phenolsulfonphthalein, 10% excretion at the end of 15 minutes, 50% total excretion at the end of two hours; creatinine, 4.30 mg.%; urine for Bence Jones protein, negative; glomerular filtration rate, $C_{In} = 49$ c.c./min.; effective renal plasma flow, $C_{PAH} = 184$ c.c./min.; filtration fraction, 0.266 (normal, 0.20).

Blood Chemical Studies: Total protein, 10.1 gm.%, with 2.6 gm.% albumin, 7.5 gm.% globulin. Repeat: total protein, 10.1 gm.%, with 2.7 gm.% albumin, 7.3 gm.% globulin. Serum chlorides, 111 mEq./L.; serum sodium, 141.5 mEq./L.; serum potassium, 5.0 mEq./L.; serum calcium, 9.7 mg.%; inorganic phosphorus, 4.05 mg.%; repeat: serum calcium, 9.9 mg.%. Oral glucose tolerance test: fasting, 89 mg.%; one-half hour, 164; one hour, 216; two hours, 102; three hours, 126; intravenous glucose tolerance test: fasting, 90 mg.%; one-half hour, 136 mg.%; one hour, 108 mg.%; two hours, 88 mg.%; three hours, 99 mg.%.

X-ray Data: Chest film showed a diffuse increase in the prominence of the vascular markings of a reticular nature throughout the lung fields. Hilar adenopathy was absent; amorphous calcium was present in the left para-aortic and hilar glands, possibly indicating an old tuberculous infection. There were no significant abnormalities of the hands and feet. On a plain film of the abdomen the liver shadow was slightly enlarged. A sialogram (figure 2) after injection of the right Wharton's duct with Pantopaque outlined a normal main duct. The subsidiary channels and canaliculi, particularly on the cephalic side of the main parotid duct, appeared to be straightened, stretched and narrowed. There was no block of the ducts. It was concluded that there was a diffuse infiltration of the parotid parenchyma. Dental films showed no abnormalities. Intravenous pyelograms showed no gross abnormalities. An upper gastrointestinal series was indeterminate.

Miscellaneous Studies: An electrocardiogram was within normal limits. Schirmer's test showed a marked decrease in tear formation. PPD was positive (3 plus at the end of 48 hours).

Endoscopies: Bronchoscopy: The bronchial tree appeared to be extremely dry, and remained so after the instillation of normal saline; all orifices were visualized and appeared to be normal. A minimal amount of secretion was aspirated from the right upper lobe orifice for culture examination.

Gastroscopy: The mucosa was of a normal orange-pink color and had a glistening, moist appearance. Three separate gastroscopic biopsies (obtained with the Benedict operating gastroscope) disclosed normal gastric mucosa. There was no atrophy or intestinalization of the glandular pattern (figure 3).

Gastric Analysis: There was no free acid in the fasting sample on two occasions. It was noted that prior to histamine the gastric contents were very scant and extremely viscid. Following histamine stimulation: 101 clinical units of acid; 28° of free HCl; 94° following histamine.

Pancreatic Function:

Methods: Duodenal drainage was accomplished using the Diamond double lumen tube according to the standard method of Dreiling and Hollander.[9] Its position in

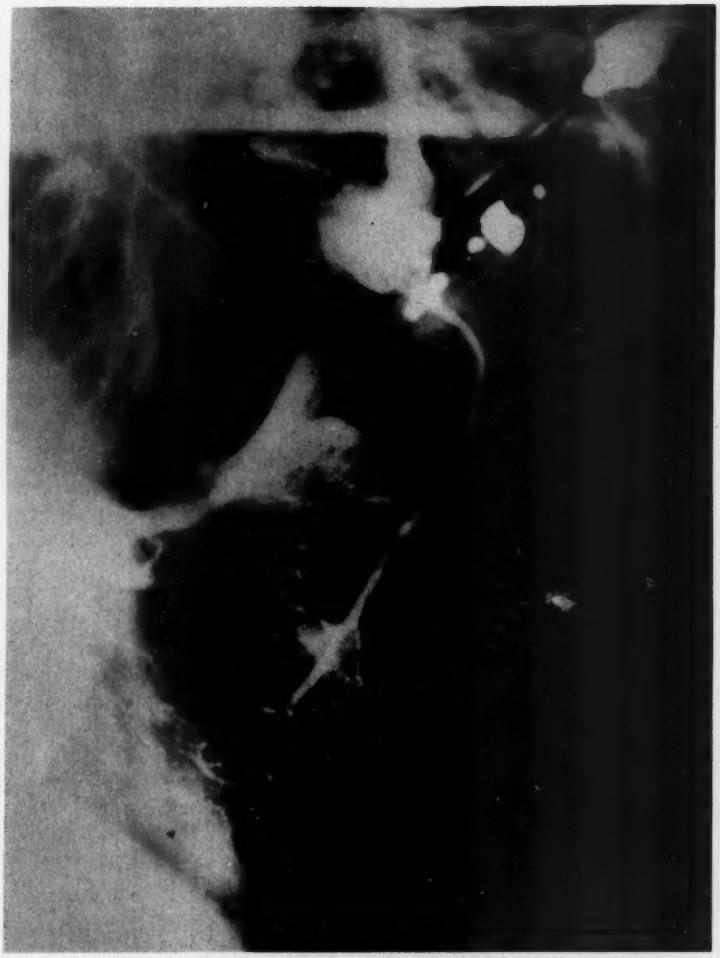

FIG. 2. Sialogram, right Wharton's duct. The main duct appears to be normal. The subsidiary channels, especially on the cephalic side, appear to be narrowed and elongated. The findings were suggestive of a diffuse parenchymatous infiltration of the submaxillary gland.

the third portion of the duodenum was checked fluoroscopically before the study. A Beckman pH meter was used to measure pH of the intestinal fluid. Duodenal diastase was determined by the method of Agren and Lagerlof.[10] The icteric index of the duodenal aspirate was used as a measure of gall-bladder function. The Secretin * used, a mixture of crystallized polypeptides free of detectable amounts of cholecystokinin and pancreozymin, causes the normal gall-bladder to take up all the bile

* Generously supplied by the Research Department of Eli Lilly & Co., Indianapolis, Indiana.

TABLE 1

Case Summary of Systemic Manifestations

Organ System	Clinical Data	Laboratory Data	Functional Tests	Radiographic Data	Histologic Study	Status Following Steroid Therapy
Salivary glands	Xerostomia, enlargement of parotid and submaxillary glands	Routine bacterial, fungal cultures of biopsied specimen: neg. Guinea pig inoculation: unremarkable. Viral studies: noncytotoxic	Diminished salivation; no change after histamine intravenously	Sialogram: minor canaliculi straightened, elongated and narrowed extrinsically	Round cell infiltration	Increased salivation, diminished inflammation
Ocular system	No visible lacrimal enlargement; diminished tear formation; dryness and burning of eyes	Fluorescein test: punctate erosion, left cornea	Schirmer's test positive; vision intact			Equivocal change in Schirmer's test
Skeletal	Intermittent migratory polyarthralgia	Normal serum Ca, P and alk. phosphatase	No limitation of joint motion	Hands and feet, ribs and spine, dental films: no significant abnormalities		
Respiratory	Intermittent dry cough		Dry bronchial mucosa visualized bronchoscopically	Diffuse nonspecific pulmonary infiltrations of a reticular nature		Relief of cough; no change in chest film
Renal	Hypertension	Azotemia, albuminuria, normal serum electrolytes	Low urine sp. gravity, diminished PSP excretions. Diminished GFR, RPF and F.F. Urinary protein excretion, 0.24 mg./min.	IVP's normal		Transient increase in azotemia

TABLE 1—*Continued*

Organ System	Clinical Data	Laboratory Data	Functional Tests	Radiographic Data	Histologic Study	Status Following Steroid Therapy
Digestive						
(a) Esophagus	Occas. dysphagia		Normal swallowing mechanism (Ba swallow)	(Upper GI Series): No lesions		
(b) Stomach	Asymptomatic; viscid, tenacious secretions		Free HCl only after histamine; pliant mucosal folds w/active peristalsis gastroscopically	Normal	Three biopsies, normal histology	
(c) Liver	Hepatomegaly	Essentially normal liver function tests; hyperglobulinemia		Plain abdominal film confirmed hepatomegaly	Liver biopsy unsuccessful	Hyperglobulinemia diminished
(d) Gallbladder			Adequate concentration after secretin; normal contraction after $MgSO_4$.			
(e) Pancreas		Fasting serum amylase elevated	Viscid duodenal secretions; low volume but normal enzyme response to secretin; prolonged elevation of serum amylase and lipase; normal oral and IV glucose tolerance	No enlargement of duodenal loop		
Hematopoietic	Splenomegaly	Normal hemogram; no elevation of ESR; Coombs' test positive		Plain film: splenomegaly	Bone marrow, slight eosinophilic hyperplasia; lymph node biopsy: normal	Coombs' test became neg.; hepatosplenomegaly disappeared
Skin	Normal sweating				Adequate sebaceous glands; chronic inflammatory cells	

that flows through the hepatic ducts, the bile-stained duodenal juice becoming colorless within a few minutes after Secretin injection. Accordingly, the bile pigment curve differentiates a diseased gall-bladder or occlusion of the cystic duct by stone or atresia.[10, 11] Adequate contraction of the viscus was evaluated by the appearance of "B" bile after $MgSO_4$ stimulation at the end of the 80-minute collection period.

Serum diastase and lipase were measured according to the methods of Somogyi [12] and Cherry and Crandall.[13] The concentration of bicarbonate was estimated by direct titration with one tenth normal hydrochloric acid. Duodenal trypsin was measured by Northrop's [14] method.

Results: The total volume of duodenal drainage was considerably diminished before and even after Secretin stimulation (total, 61 c.c. after 60 minutes—table 2).

The icteric index curve of the duodenal collections was normal and indicated a normally functioning gall-bladder that contracted well after storing bile.

TABLE 2

May 24, 1954

	Before Secretin	10′ after Secretin	20′	30′	40′	50′	60′	60′ Total	60′ Total Normal Value	80′
Amount	3 c.c.	1 c.c.	26 c.c.	7 c.c.	11 c.c.	10 c.c.	6 c.c.	61 c.c.	75–400 c.c.	19 c.c.
pH			8.38	8.86	8.6	8.4	8.52			7.92
Trypsin (unit/c.c.)			0.7	0.4	0.7	0.5			0.6–3.2 unit/c.c.	0.6
Diastase/c.c. Diatase, total amount	140.5 421.5	140.5 140.5	245 6,370	227 1,589	251 2,761	219 2,190	251 1,506	14,556	12,000–14,200 units	234.5 4,455.5
Icterus index (units)	9.3		1.4		6	5.5	5.5			35
Bicarbonate (mEq./L. $NaHCO_3$)	56		85	100	109	81	63	438	75–130 mEq./L.	

Serum

	Before Secretin	30′ After Secretin	60′ After Secretin	90′ After Secretin	Normal Values
Serum diastase	336	306	306	381	80–150 units
Serum lipase	1.2	1.9	1.9	1.8	0.2–1.5 c.c. 20/N NaOH

The fasting serum amylase was considerably elevated prior to stimulation and might have been related to the enlargement of the salivary glands; however, the serum lipase remained elevated 90 minutes after Secretin stimulation, possibly reflecting an increased pancreatic response.

The pancreatic enzyme response to Secretin was normal. The elevation of bicarbonate was adequate, and was reflected in the rise of pH of the duodenal contents.

Bacteriology: Three gastric aspirations for acid-fast bacilli were negative, and guinea pig inoculation was noncontributory. Urine culture, no growth; blood culture, no growth. Cultures of bronchoscopic washings were negative for acid-fast bacilli on guinea pig inoculation. Culture of submaxillary node biopsy: routine and fungus cultures, no growth. No lesions were produced in a guinea pig after inoculation. Tissue culture for virus: no cytopathogenic effect was observed in HeLa cell tubes.*

* The authors are indebted to Dr. Dorothy Horstman and Dr. James Neiderman for their kindness in performing tissue culture studies.

Hematology: Total eosinophil count, 344 per cubic millimeter. Coombs' test, positive initially; post-treatment: direct, negative; indirect, negative. Prothrombin time, 87% of normal control; bleeding time, 2 minutes 30 seconds; clotting time, 4 minutes 15 seconds. Heterophil test, negative. Sternal marrow: slight eosinophilic hyperplasia of the bone marrow.

Course in Hospital: It was noticed repeatedly that the gastric aspirate appeared to be very viscid and occluded the nasogastric tube. Following the routine histamine injection the gastric juice became very clear, abundant and watery. At the same time the patient volunteered that his salivation seemed to have increased, with a lessening of his usual dry mouth. Accordingly, an empiric three-day course of intravenous histamine was given. There was, however, no obvious benefit by measurement of salivary volume before and after infusion, and the infusions were discontinued.

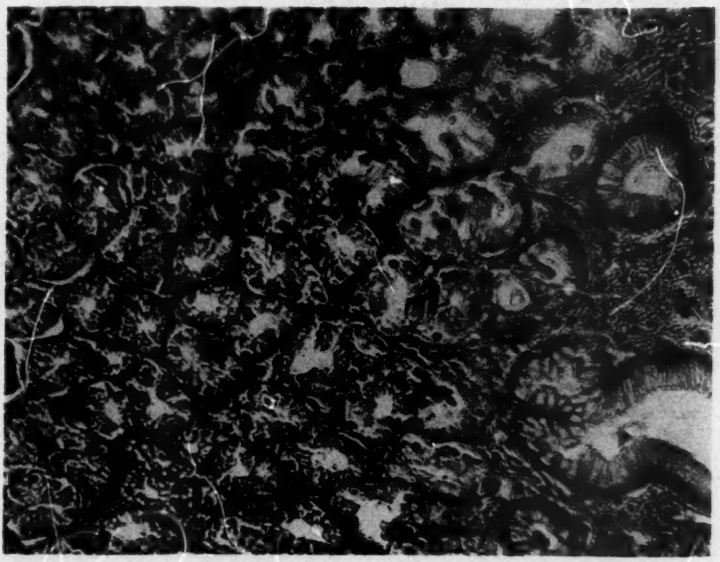

FIG. 3. (×200) Gastric mucosal biopsy. The glandular pattern appears to be intact. The chief and parietal cells occur in the proper ratio. Intestinalization or atrophy is not present. A junctional area between a crypt and neck gland is seen in the lower right corner.

Numerous diagnostic studies were uneventfully performed during hospitalization. In addition to those outlined above, the following biopsy specimens were obtained: *

1. Axillary node biopsies: hyperplastic nodes, without granulomata.

2. Gastric biopsies: A normal body glandular pattern was seen. There was no atrophy or intestinalization. The crypts and neck glands in some areas contained a little secretion. The interstitial tissue between the foveae and body glands was not infiltrated except for the presence of a few small to moderate lymphocyte aggregations above the muscularis mucosae. Impression: gastric mucosa, without atrophy (figure 3).

* The authors are indebted to Dr. Raymond Yesner and Dr. William Wedemeyer, Veterans Administration Hospital, West Haven, who examined the specimens.

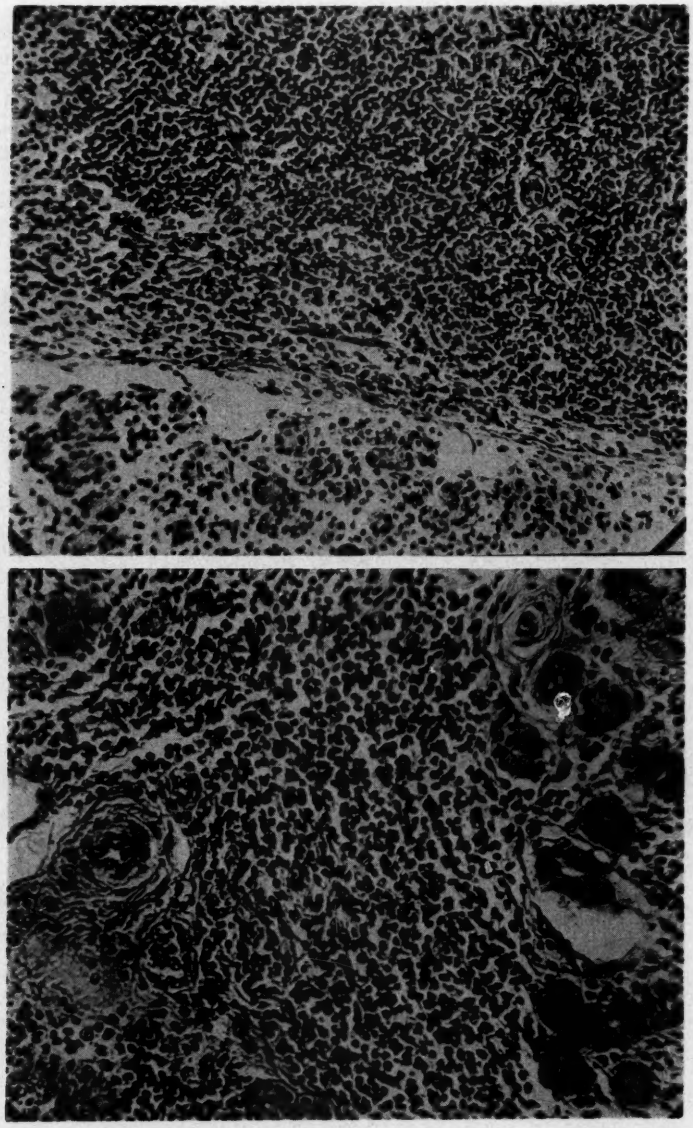

FIG. 4. A. (*above*) (×100) Low power view of the right submaxillary gland, representing loss of architecture and replacement by chronic inflammatory cells. B. (*below*) (×200) The inflammatory cells are largely lymphocytes and plasma cells, with some eosinophils. No myo-epithelioid cells are evident. Note that some lobules are untouched by the process.

3. Biopsy of the anterior inferior pole of the right submaxillary gland (pretreatment): Glandular elements were surrounded and compressed by large and small mononuclear cells which densely infiltrated the interstitium. Most of the cells were lymphocytes, but many were plasma cells. Polymorphonuclears and eosinophils were not prominent. There was no necrosis or fibrosis. Mucus secretion was evident but greatly diminished. No myo-epithelioid cells were seen. Impression: chronic inflammation of the salivary gland (figure 4).

4. Left submaxillary gland (21 days after the initiation of steroid therapy): There was a widespread chronic inflammatory change, manifested chiefly by interstitial lymphocytic infiltration, particularly about the ducts. Plasma cells were intermingled with the lymphocytes. There were some atrophy and fibrosis of the parenchyma. Fibroblasts were present in the more active areas. In general, there were somewhat less marked inflammatory changes in this specimen than previously.

FIG. 5. (×200) Left submaxillary gland, showing an area free of inflammatory exudate, with normally secreting glands. Mucin is seen but is diminished.

There were some areas which were quite free of these alterations, with some normally secreting glands, although mucin secretion was generally diminished (figure 5). Skin (adjacent to a small epidermoid cyst which was excised): The section of skin contained many sebaceous glands and showed senile elastosis with many chronic inflammatory cells.

On June 1, 1954, the patient was started on a course of intravenous ACTH (25 mg. in 5% dextrose and water over an eight- to 10-hour period). Within two days of initiation of this therapy there was a marked improvement in the clinical picture. The patient's salivary glands began to diminish in size, particularly the parotid glands, and he was able to produce a good deal of saliva, which he had not been able to do previously. The troublesome dry cough, present since admission, disappeared. ACTH was discontinued after 11 days, at which time the patient was

asymptomatic except for continued dryness and irritation of the eyes. Thereafter he was gradually switched to oral cortisone and was maintained on 12.5 mg. twice a day for six weeks. He stated that he was markedly improved, and that his only remaining symptom was conjunctival irritation. Ophthalmologic consultation revealed diminished lacrimal secretion and a punctate erosion of the cornea of the left eye, with a slight amount of tenacious secretion. Sodium sulfacetimide with ½% methylcellulose drops was prescribed and the patient was discharged. Repeat studies (June 11, 1954) after ACTH therapy disclosed: total protein, 6.69 gm.%, with 2.3 gm.% albumin, 4.39 gm.% globulin; nonprotein nitrogen, 80 mg.%; urea, 55.2 mg.%. After minimal doses of cortisone, (June 16, 1954), nonprotein nitrogen was 65 mg.%; urea, 40 mg.%; creatinine, 3.15 mg.%.

The patient has remained well during the last three years and has had no complaints.

Comment: Certain unusual features of this case, such as hepatosplenomegaly, pulmonary infiltration, hyperglobulinemia and azotemia, strongly suggested the diagnosis of sarcoidosis. However, biopsies of the salivary glands, lymph nodes and bone marrow failed to reveal any evidence of granulomata. In addition, the tuberculin test was strongly positive and there was no hypercalcemia or hypercalciuria.[15] An attempt at liver biopsy was unsuccessful and was not repeated, so that hepatic sarcoid infiltration[16] could not definitely be ruled out, although liver functions were normal. There seems to be adequate histologic data to rule out sarcoidosis in the present case. Gruber[17] recently reported a case of sarcoidosis of the lacrimal glands displaying Sjögren's syndrome.

Discussion

A summary of the systemic manifestations of this case is outlined in table 1. That the "sicca syndrome" is a clinical reflection of diffuse involvement of the eccrine glands[6] is borne out by this case.

Salivary Glands: The salivary glands were functionally able to secrete some saliva, although at a low level (2 to 5 ml. in a 10-minute collection while the patient was chewing gum; controls, 18 to 20 ml./10 min.) This has been accurately studied by others,[18, 19, 21] who found low initial volumes in their cases, with no response to pilocarpine or the chewing of paraffin wax. Cadman and Robertson[19] measured the parotid gland amylase output and found it to be markedly reduced (9 units/ml.; normal, 100 to 150 units/ml.), with no response to pilocarpine. Iodide could not be found in the saliva after a dose of potassium iodide.[20] Gurling[21] found no pus cells in smears from the parotid ducts in his reported case. *Streptococcus viridans* and *Neisseria catarrhalis* were cultured. We were unable to culture any bacteria, fungi, acid-fast bacilli or virus from a submaxillary gland biopsy, nor did guinea pig inoculation with homogenized specimen produce any noteworthy histologic lesions.

Further studies using frozen submaxillary gland tissue specimens from this case for virus detection by present day technics[22] failed to disclose any cytopathogenic effect, even after blind passage.

The normal electrolyte content of saliva has been determined.[23] The chloride content in our patient's saliva was found to be slightly diminished (38 mEq./L.).[24]

The histologic examination presented here showed widespread chronic inflammatory changes, manifested chiefly by interstitial lymphocytic infiltration

periductally, confirming earlier reports.[4, 6] This explains the extrinsic narrowing of the minor canaliculi visualized by the sialogram (figure 2). Previous reports [19, 25] have shown a similar pattern, depending upon the stage of parenchymal involvement. Parret's [25] reproductions of 10 sialograms indicated good correlation with the extent of the inflammation and subsequent atrophy; in some, cavity formation due to the loss of structure was noted. Parret [26] classified the stage of illness according to the intensity of the destructive process as noted on sialograms. An excellent review of the subject of sialography has been presented by Rubin and Holt.[27] They advocate "emptying" phase films for better delineation.

Ocular System: Henderson [28] studied 280 reports of cases of keratoconjunctivitis sicca, of which 86% concerned Sjögren's syndrome, and outlined the various eye symptoms and signs usually seen. In our case, tearing was essentially absent before and after treatment with intravenous histamine and steroids. This lack of response to steroids has been the common experience.[19, 21, 29] The absence of lacrimal gland enlargement may represent irreversible destruction of parenchymal tissue, as described previously.[8] Balik,[30] however, demonstrated that the sodium chloride concentration of lacrimal fluid in pathologic cases remained unchanged despite diminution of the hydrolyzed protein level in tears. The latter may be due to decrease in mucin production, the former due to the body's constant isotonic state under most circumstances.

Skeletal System: Although migratory polyarthritis was an initial symptom, it did not reappear after steroid therapy. A skeletal survey showed no bony lesions, nor were there dental caries [18] clinically or by dental radiographic studies.

Respiratory System: An intermittent dry cough in this patient seemed to be related to the dry mucous membrane visualized bronchoscopically. The chest x-ray showed a diffuse reticular nonspecific infiltration which was not associated with hilar adenopathy. These signs were also found by Ellman and Weber.[8, 18] Obstructive collapse of a lung lobe has been reported recently.[31]

Renal System: Azotemia and mild albuminuria were evident, associated with an inability to concentrate urinary specific gravity over 1.010, diminished filtration fraction, and a reduced effective renal plasma flow. The only known report of the kidney histology in Sjögren's syndrome is Ellman and Weber's autopsied case,[8] who showed slight thickening of the glomerular capillary basement membrane and some swelling and necrosis of the tubule cells, "probably postmortem autolysis." Transient hypertension was present in our case but responded to bed-rest prior to any definitive treatment. Intravenous pyelograms, Sulkowitch's test and urine cultures were noncontributory. We hesitate to ascribe the renal abnormalities to some subtle systemic relationship to Sjögren's syndrome without any histologic data, but it merits future study, perhaps by kidney biopsy.

Digestive System: Esophagus: The swallowing reflex was not involved functionally, although there was some mild dysphagia, presumably due to dryness of the esophageal mucosa, as mentioned in other reports.[8, 32]

Stomach: The fasting gastric secretions were found to be viscid and diminished in volume, as reported by Harrington and Dewar [33] and Gurling.[21] However, adequate free hydrochloric acid was present after histamine stimulation.

Achylia gastrica has been reported.[8] Weber [34] reported the presence of small amounts of pepsin after histamine.

To our knowledge, the gastroscopic biopsies obtained in the present case are the first to be reported in the literature. The absence of gastric glandular involvement was also noted in the postmortem report by Ellman et al.[8]

Liver: Hepatomegaly, as in this case, has been described previously.[8, 19, 21] Our attempt to obtain a liver biopsy was unsuccessful. Earlier authors [8, 18, 21, 33] have reported essentially normal liver biopsies; several cases [8, 18] were associated with a pulmonary picture suggestive of sarcoidosis, as in our case. Cadman and Robertson's second case, a 54 year old female, had been jaundiced for six weeks and showed portal fibrosis. Liver function tests in our case were essentially normal except for the presence of marked hyperglobulinemia; this decreased considerably after the institution of steroid therapy, and conformed to Cadman's report.[19]

Gall-bladder: The gall-bladder concentrated bile normally during the Secretin test and contracted well after the administration of a cholegogue (25% solution of magnesium sulfate).

Pancreas: The pancreas, like the stomach, initially excreted only small amounts of a viscid secretion, but a normal increase of trypsin, diastase and bicarbonate concentrations in the duodenal aspirates occurred after chemical stimulation. Weber [34] had previously suggested that a test for pancreatic insufficiency be done to rule out involvement of this organ in the "sicca syndrome." Unfortunately, the autopsy case cited above [8] showed postmortem autolysis and could not be evaluated. An initial serum diastase elevation was noted which persisted. There were no associated abdominal complaints clinically, nor was there widening of the duodenal loop radiographically to suggest an indolent pancreatitis involving the head of the pancreas. Although salivary gland enlargement was present, it is difficult to reconcile the low salivary volume output with the high serum levels, as might be evident in some cases of parotitis (without pancreatic involvement). Warren [35] reviewed the origin of the elevated serum amylase and lipase occurring in mumps, and pointed out our lack of knowledge in this matter. Glucose tolerance curves showed no defect in intestinal absorption or utilization of carbohydrate after both oral and intravenous administration. While Weber [34] has pointed out that an insulin-like product has been extracted from submaxillary tissue, hypoglycemia was not evident four hours after glucose administration in our patient.

Hematopoietic: The increased erythrocyte sedimentation rate repeatedly reported in the literature may be only a reflection of the rheumatoid state in an active form. Our patient's polyarthralgia was not active when his erythrocyte sedimentation rate was normal during the hospitalization.

Bone marrow aspiration showed slight eosinophilia. This was also seen in the peripheral blood (8 to 11%), and may be associated only with an eosinophilic inflammatory exudate in the tissue specimens available, as in Sjögren's autopsied cases.

The significance of one positive Coombs' test is not clear, but may be a reflection of the hyperglobulinemia. It is of interest that the antiglobulin test became negative following steroid therapy and that at the same time there was a considerable decrease in the plasma globulin.

Hypochromic microcytic anemia associated with stomatitis and cheilosis [32]

has been stressed as an integral part of Sjögren's syndrome. The normal hemogram found here may reflect only the lack of debilitating symptoms during the patient's observed stage of illness.

Skin: Alteration of normal sweat mechanism, noted in other reports,[36, 8, 33] was not observed in this case. Examination of a small section of this patient's skin, removed coincidently for an epidermoid cyst of the nose, showed adequate sebaceous glands. There was no collagenous abnormality suggestive of scleroderma.[33] The vascular disorders of telangiectasia,[37, 38] acrocyanosis [39] and Raynaud's phenomenon [3, 4, 34] reported in other cases were not present in our patient.

Miscellaneous Studies: Serum electrolyte studies were normal. Sheldon [37] found unexplained hypotension in his case without demonstrable adrenal calcifications. Bossalino [40] expressed the opinion that the syndrome is due to adrenal insufficiency. However, Pond [41] studied 11 females (36 to 71 years of age) with Sjögren's syndrome and found that all had consistently lowered urinary 17-ketosteroid values (1 to 3 mg./24 hours; normal range, 4 to 14 mg./24 hours). Fractionation by absorption chromatography showed a lowering of all eight fractions, in particular the beta fraction, which is generally considered to be an indication of over-all adrenocortical activity. He concluded that these studies do not indicate any endocrine abnormality in the disease, but reflect the debilitating nature of the disease and suggest a potentially normal adrenocortical function. Other cases of Sjögren's disease in which 17-ketosteroid assay has been recorded had a low value [21] or a normal value.[42]

Porphyrinuria was found in two patients with Sjögren's syndrome by Franceschetti.[43] This was not tested for by us.

Pathogenetic Aspects

It is common practice to attempt to understand the pathophysiologic nature of a disease process by histologic study of the diseased tissue. In 1953 Morgan and Castleman [6] reported their results of a detailed investigation of 18 cases of Mikulicz's disease. They concluded that the primary defect in this disease is a replacement of the acinar parenchyma by lymphoid tissue, with secondary intraductal proliferation of epithelial and myo-epithelial cells. They suggested that the condition is probably a manifestation of the more generalized process of Sjögren's disease. This impression was reëmphasized by Morgan [7] in a later report on the clinical re-investigation of these cases and of Sjögren's original material. Although such studies shed a great deal of light on the pathology of Sjögren's disease, they do not satisfactorily explain the pathogenesis—as has been pointed out by Morgan and Castleman. The presence of large numbers of lymphocytes in the glands of these patients may be the result and not the cause of a disease process. The analogy between Sjögren's disease and Hashimoto's struma, in which there is intense invasion of the thyroid gland by lymphocytes, has already been commented on by others.[6, 44] Lymphocytic infiltration of various tissues occurs in many disease processes, i.e., infections, especially of viral nature (lymphocytic choriomeningitis), degenerative diseases (diabetes and cirrhosis), and conditions of obscure etiology (aplastic anemia). The degree of lymphocytic invasion in these conditions may at times be striking. It is of particular importance to note that our patient improved within a few days following small doses of adrenal steroids and was able to salivate again, yet biopsy of

the gland following therapy showed no great change in the lymphocytic infiltration.

The results of the functional studies done on our patient have suggested to us, as to others, that Sjögren's disease may represent an alteration in the physiology of the secretory glands of the body. We were able to demonstrate diminished base line secretions of the lacrimal and salivary glands, bronchial mucosa, stomach and pancreas. In the latter two organs it was of interest that during a "resting" phase the volume of secretions was decreased and yet the glands were able to respond well to chemical stimulation. This might suggest that the secretory cells in Sjögren's disease may function at a low "base line" rate while the reserve function in the early phase of the disease is unimpaired. On the other hand, those tissues which were in the far advanced phase of the disease were unable to respond to stimulatory mechanisms (lacrimal and salivary glands). The etiology of the kidney disorder in this patient remains obscure, and future studies in other cases will be necessary to determine whether the renal involvement is directly related to the general process in Sjögren's disease. The decreased bronchial secretion that was noted on bronchoscopic examination may have accounted for the patient's chronic nonproductive cough, and the diffuse pulmonary infiltrate might have represented inspissated terminal bronchiolar secretions. This raises the question of a possible relationship of Sjögren's disease to fibrocystic disease of the pancreas, which appears to be a generalized disease of the exocrine glands.[45] The concept that the symptom complex described by Sjögren may represent an "eccrine disease" appears quite plausible, but further physicochemical studies are needed to substantiate this.

Therapy

It is not the purpose of this paper to review all the many forms of therapy that have been suggested for Sjögren's disease. The fact that our patient had symptomatic and objective evidence of increased glandular secretions following the injection of histamine during a gastric analysis suggested the use of this drug for treatment. A brief trial of intravenous histamine was attempted, but without clinical benefit. A perusal of the literature reveals that corticoid therapy has been helpful in some cases [19, 21] but failed in others.[29, 46] Our patient was greatly benefited by steroid therapy, initially given as intravenous ACTH and later changed to oral cortisone for six weeks. The salivary gland swellings subsided (figure 1) and again saliva was produced. There was relief of cough and arthralgia, hepatosplenomegaly subsided, the hyperglobulinemia diminished, and Coombs' test became negative. Although there was no subjective or objective improvement in lacrimation by Schirmer's test, and the conjunctivitis persisted, no other symptoms have appeared and the patient has remained well for the last three years.

Summary

1. A case of Sjögren's syndrome occurring in a young male is reported. Symptoms of dry mouth, sore eyes, nasal stuffiness, bilateral facial swelling and polyarthralgia were present.

2. Physiologic studies showed that the stomach and pancreas, like the salivary and lacrimal glands, excreted only small volumes of a thick, viscid secre-

tion. However, the pancreas and stomach responded to chemical stimulation in a normal fashion.

3. Endoscopic findings of the stomach and bronchi are reported.

4. The histopathology of biopsied submaxillary glands before and after steroid treatment is described. Culture of a specimen of submaxillary gland failed to grow any bacteria or fungi. Inoculation in a guinea pig produced no visceral lesions. Tissue culture studies for virus showed no cytopathogenic effect.

5. Renal disease was present, manifested by azotemia, labile hypertension, hyposthenuria, diminution in glomerular filtration, effective renal plasma flow and filtration fraction.

6. Rapid clinical improvement followed administration of ACTH and cortisone therapy.

Summario in Interlingua

Se presentava un juvene adulto con le gravamines de siccitate buccal, tusse, oculos dolorose, congestion nasal, polyarthralgia, e tumescentia bilateral del glandulas salivari. Le studio del caso resultava in le constatation que multe systemas de organos del patiente esseva afficite.

Es describite in le presente reporto varie examines laboratorial, functional, e radiographic.

Esseva constatate azotemia renal con hyposthenuria, reducite filtration glomerular, reducite fluxo efficace de plasma renal, e reducite fraction de filtration. Le roentgenogramma thoracic monstrava un aspecto reticular del pulmon. Un desiccate mucosa bronchial esseva visualisate bronchoscopicamente. Le secretiones gastric esseva viscose e tenace, sed le examine gastroscopic revelava nulle anormalitates. Biopsias gastric esseva normal. Le volumine del drainage duodenal esseva reducite ante e post secretina, sed le responsa de enzyma pancreatic esseva normal. Le nivello de amylase in le sero esseva elevate. Hepatosplenomegalia esseva associate con normal tests del function hepatic, excepte que hyperglobulinemia esseva constatate e que le test de Coombs esseva positive. Le examine del medulla ossee revelava leve grados de hyperplasia osinophilic.

Sialogrammas monstrava restriction canalicular, presumibilemente relationate al infiltration de cellulas rotunde que esseva trovate biopticamente.

Culturas de un specimen de glandula submaxillar resultava in nulle crescentia de bacterios, fungos, o viruses. Le inoculation in porcos de India produceva nulle lesiones visceral.

Le therapia a ACTH e cortisona resultava rapidemente in melioration clinic con remission de symptomas de persistentia durante plus que tres annos, sed un biopsia del glandulas salivari brevemente post le therapia monstrava nulle considerabile alteration del infiltration lymphocytic.

Le resultatos del studios functional suggere de novo que le syndrome de Sjögren pote representar un alteration in le physiologia del glandulas secretori del corpore. Studios additional es indicate pro corroborar le impression que le complexo de symptomas representa un "morbo eccrin."

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FATAL FUNGUS INFECTION IN SARCOIDOSIS: REPORT OF TWO CASES TREATED WITH ANTIBIOTICS AND CORTISONE*

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Reports of fatal fungus infection following antibiotic and hormonal (ACTH and cortisone) therapy are continuing to appear in the literature. This is due in part to improved cultural and animal inoculation and histopathologic technics,

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increasing interest in fungi, and to the greater incidence and virulence of the fungi because of extensive antibiotic and hormonal therapy.[1-5] Zimmerman [1] has emphasized also the tendency of certain disseminated fungus infections to become associated with such primary disease as aplastic anemia, the lymphomata, leukemia, diabetes, tuberculosis and cancer.

In 1952 the first instance was reported of fungus infection causing lung abscesses in a patient with sarcoidosis treated with antibiotics.[6, 7] The two cases herein reported received cortisone in addition to antibiotics. The possibility of fungus infection complicating sarcoidosis in such instances may no longer be of academic interest: the recent discovery of a new antibiotic agent believed to be antifungal may have therapeutic significance.

Case Reports

Case 1. Sarcoidosis, Pulmonary Insufficiency and Hypertension, and Nocardiosis.

A 38 year old Negro female teacher was referred by Dr. Marian Tyndall on August 29, 1944. The patient stated that eight months earlier a routine chest x-ray by the Gary, Indiana, school department showed pulmonary disease. Subsequently, tuberculin and sputum studies were "negative." However, the abnormal chest x-ray findings persisted. The patient had always considered herself well, although she was subject to frequent chest "colds." Three years earlier, during a rather severe cold, she had had "pleurisy" in the right lower axilla which lasted a few days and never recurred. Two years prior to admission, minute nontender nodular masses appeared about the nose and eyes.

Physical examination revealed a well developed and well nourished Negro woman in no distress. Minute papular nodules were present over the alae nasi and face. No masses were felt in the cervical, axillary or inguinal regions. The lungs were clear and the heart examination, including the electrocardiogram, was normal. The blood pressure was 120/80 mm. of Hg. The chest x-ray revealed some right mediastinal widening. Mottled nodular densities were present at both hili and extended to the mid and lower lung fields. Tuberculin tests up to 1 mg. O.T. were negative. Several sputum and gastric washing specimens were negative for acid-fast bacilli on smear and culture.

On the next visit, two years later (August 16, 1946), the patient stated that she had been employed steadily for the last two years, but for nine months had been troubled by a persistent, slightly productive cough, wheezing and dyspnea on exertion. Again the chest was clear on physical examination and the roentgenogram showed the same areas of infiltration. Over a year later (December 20, 1947), she reported that the cough, wheezing and dyspnea had continued but had not prevented her from working. She called attention to a cluster of small nodules about the alae nasi which had become tender. The chest examination revealed no abnormal findings. However, the chest x-ray showed increase of the nodular lesions about the hili, mid and lower lung fields. Biopsy of a nose lesion showed Boeck's sarcoid.

A year later the patient reported that cough and expectoration, wheezing and dyspnea had continued. At this time expiratory wheezing was audible, and many musical râles were also elicited. At the next visit (June, 1950), the patient reported that the cough and expectoration, wheezing and dyspnea had increased. Expiratory wheezing and sonorous râles were again audible, and the chest x-ray (figure 1) showed widespread infiltration of the lower two thirds of both lung fields, with bilateral rounded areas of translucency in the midlung regions suggestive of cavities or bullae.

The patient was hospitalized on August 16, 1950, and again tuberculin skin tests were negative. Sputum and gastric washings, smears and cultures were also negative for acid-fast bacilli. Blood and bone marrow examinations were normal; the albumin globulin ratio was 4.2/2.7. The electrocardiogram showed no deviation of the electrical axis; the heart was in a semivertical position. Angiocardiography (figure 2) on August 25, 1950, revealed some enlargement of the pulmonary artery and branches consistent with pulmonary hypertension. There was also marked distortion of the segmental blood supply to the lower lobes. Cardiac catheterization done by Dr. Daniel S. Lukas on August 28, 1950, revealed moderate to marked pul-

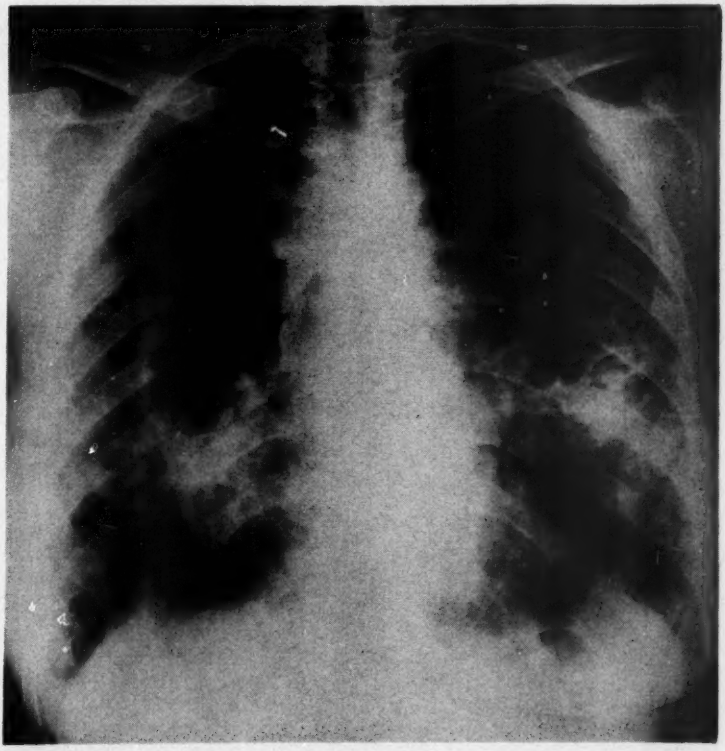

FIG. 1. *Case 1.* Widespread bilateral sarcoidosis of the lungs with hilar and mediastinal involvement. Note the bullae at mid and lower lung fields.

monary hypertension with diminution of the cardiac reserve. The pulmonary artery pressure at rest, with a normal cardiac output, was 46/17 mm. Hg, with a mean pressure of 31 mm. Hg (normal, 25/8; mean, 15). During exercise the cardiac output increased very slightly but the pulmonary arterial pressure increased to 75/23 (mean, 45). The pulmonary "capillary" (wedge) pressure was normal (7 mm. Hg) at rest, and indicated that the high pulmonary arterial pressure was due to increased pulmonary vascular resistance rather than to left ventricular failure.

From September 1, 1950, to September 14, 1950, the patient was treated with 50 mg. of cortisone every six hours, and received a total dosage of 2.8 gm. During

treatment the wheezing decreased, pulmonary function improved and the patient felt better; however, no improvement in the chest x-ray findings was seen.* She was discharged on September 21, 1950.

A year later (July 9, 1951), the patient reported that following discharge she had felt well and for six months had been able to resume teaching. Then she had

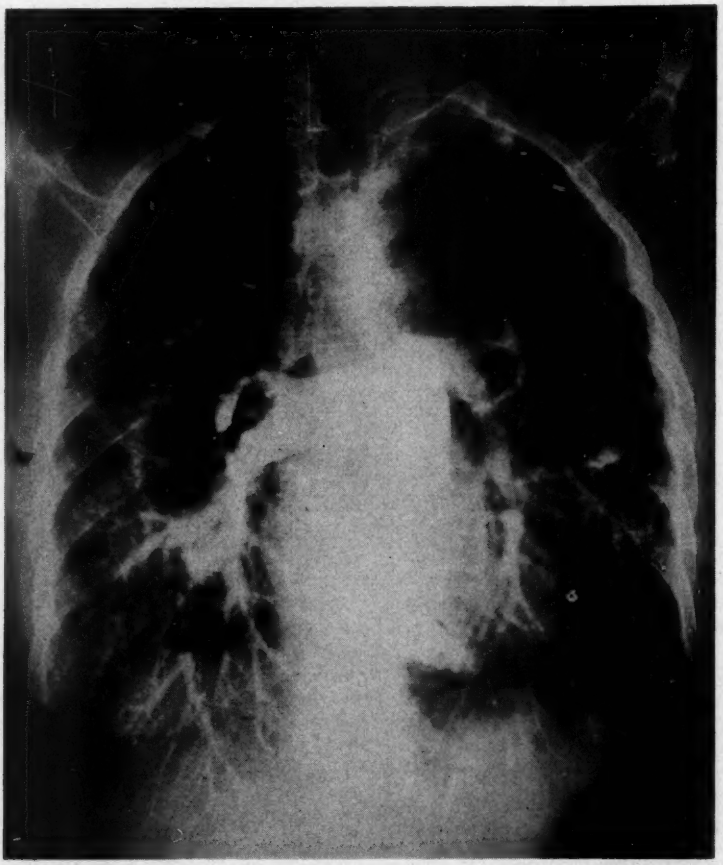

FIG. 2. *Case 1.* Angiocardiogram showing an enlarged pulmonary artery and branches. (Pulmonary hypertension was found on cardiac catheterization.) The pulmonary arterial blood supply to the upper lobes is diminished, while the lower lung field pulmonary circulation is crowded and distorted.

developed a severe "cold" and a diagnosis of "virus pneumonia" was made. Aureomycin and penicillin were prescribed and she was confined to bed until January, 1951. She tried to work but in a month became worse and went to Phoenix, Arizona, for rest and treatment. Aminophylline and antibiotics caused some subsidence of the

* The details of the response to cortisone (patient, "L. M.") are included in a publication by Dr. Daniel S. Lukas.[8]

cough, but weakness, blood-streaked sputum and lassitude persisted. Examination at the New York Hospital Clinic (July 9, 1951) revealed moderate dyspnea and generalized expiratory wheezing. The chest x-ray again showed widespread infiltration of the lower lung fields, with excavations in the midlung fields. She subsequently returned home.

A communication from a Gary, Indiana, hospital reported that on December 17, 1951, the patient came to the emergency department complaining of dyspnea, and expectoration of blood and mucus, and was admitted to the hospital. Moist and

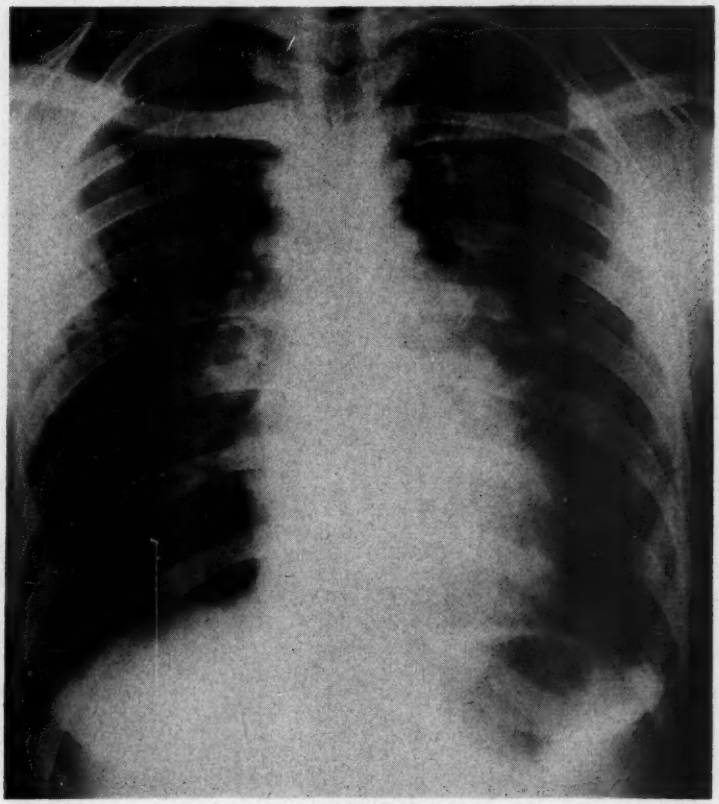

FIG. 3. *Case 2.* Boeck's sarcoid of the lung, showing hilar and right upper lobe involvement.

musical râles were heard throughout the entire chest. She was treated with penicillin, streptomycin and hormones. (The dosage could not be ascertained.) She seemed to improve but on January 3, 1952, developed a stiff neck and a positive Kernig's sign and lapsed into coma. She died on January 16, 1952. Complete autopsy findings were not obtained but the following details were learned: There was marked enlargement of all lymph glands of the mediastinum; 5 to 7 cm. cavities were present in each lung, and there were abscesses in both the right and the left

sides of the brain, approximately 2 to 4 cm. in diameter. Smear and cultures from the brain abscesses revealed *Nocardia asteroides.**

Case 2. Sarcoidosis, Pulmonary Insufficiency, and Septic and Fungus Abscesses of the Lung.

A 32 year old Negro housewife was admitted on November 7, 1954, with complaints of cough, expectoration, dyspnea and fever. Four years earlier she had had a sudden onset of hemoptysis, and after a chest x-ray at a Board of Health chest

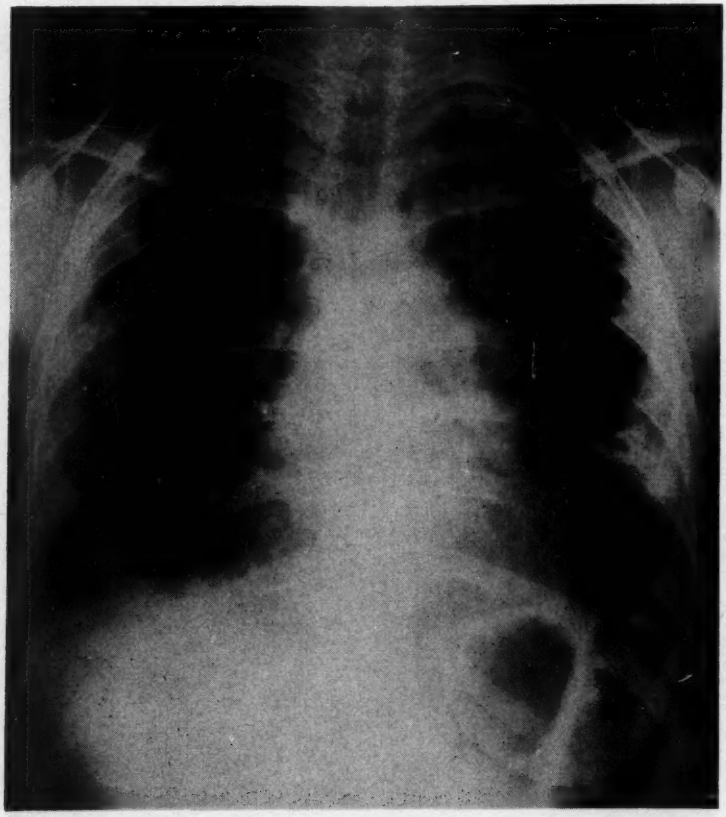

FIG. 4. *Case 2.* Two years later, there is widespread bilateral pulmonary hilar and mediastinal sarcoidosis. The lungs contain multiple small, cystlike lesions.

clinic had been told that she had disease of the lungs. Subsequently she became asymptomatic and was referred to the Out-Patient Department of The New York Hospital, where a chest x-ray (figure 3) revealed marked mediastinal and hilar adenopathy, with diffuse pulmonary infiltrations of the right upper lung. Nodular lesions were noted on the face, and biopsy revealed a granulomatous lesion with giant cells characteristic of Boeck's sarcoid. Tuberculin skin tests were negative up to 1 mg.

* Courtesy Dr. Milton May, Gary, Indiana.

dilution, and several sputum and gastric specimens (smear and culture) were negative for acid-fast bacilli.

Two years prior to admission she had had another hemoptysis. The chest x-ray (figure 4) showed increase in the pulmonary infiltrations, the left upper lung field also being involved. Eighteen months prior to entry she had been admitted to another hospital because of still another bout of hemoptysis, and a smear of the sputum was reported to be positive although tuberculin skin tests were negative. After a twelve day stay she returned to The New York Hospital clinic. A year prior to admission the patient was admitted to the hospital because of dyspnea and hemopty-

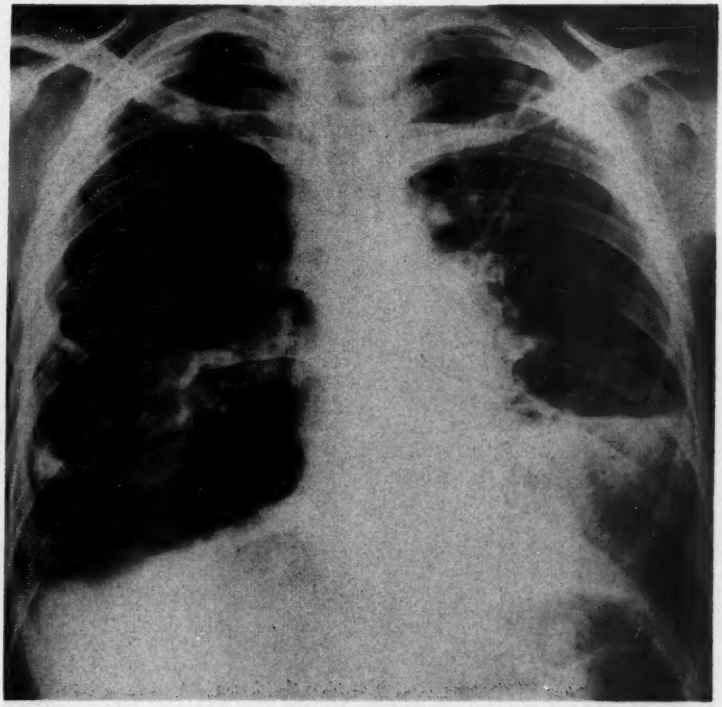

FIG. 5. *Case 2.* Two months later huge cysts occupy both lungs. Fluid is also present in a large cyst at the left base.

sis. She was then in the third trimester of pregnancy and after two months had a full term, normal delivery. There was increase in the pulmonary lesions. Five sputum cultures were negative for acid-fast bacilli, and again tuberculin skin tests were negative. Afterward, the patient was able to be at home and was well except for dyspnea on exertion. Two weeks prior to her final admission she had a "cold," with cough and expectoration. She visited the clinic and was found to be febrile; Aureomycin was prescribed. However, the cough, expectoration, dyspnea and fever persisted and hospital entry was advised.

On examination on November 6, 1954, the patient was a thin, well developed Negro woman with mild dyspnea and a temperature of 39.1° C. Several pigmented,

nontender, 2 to 3 cm. papular nodules were present on the face. There were no cervical, axillary or inguinal lymph nodes. Examination of the chest revealed expiratory wheezing, rhonchi, and moist and musical râles all over the thorax. The heart was normal, and the pulmonic second sound was greater than the aortic second sound. Laboratory examinations were as follows: hemoglobin, 13.6 gm./100 c.c.; erythrocytes, 4.9 m./cu. mm.; hematocrit, 39%; white blood count, 16,000/cu. mm.; sedimentation rate, 45. The tuberculin and histoplasmin skin tests were negative. The urine was normal; the albumin globulin ratio was 4.1/2.8. A sputum smear contained many pneumococci, and culture showed many bacteria and *Monilia albicans*. The electrocardiogram was normal. The vital and maximal breathing capacities were well below the predicted levels and did not improve after use of a bronchodilator.

While the patient was in the hospital her high fever persisted. Isoniazid, 250 mg. daily, Aureomycin, penicillin and dihydrostreptomycin were prescribed, but fever, cough and expectoration persisted. The chest x-ray (figure 5) showed the development of multiple, thin-walled, cystlike areas bilaterally, more on the right.

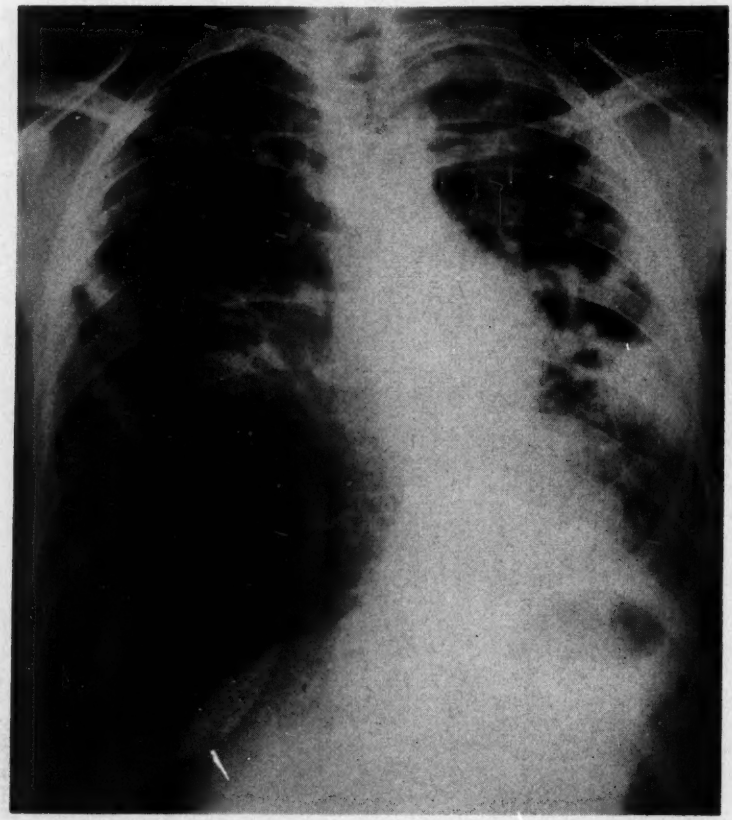

FIG. 6. *Case 2.* Two and a half months prior to death, a spontaneous pneumothorax occurred at the right base. Note the shift of the heart and mediastinum. Pneumonia is present above the right pneumothorax and at the left midlung field.

FIG. 7. *Case 2.* Photograph of gross specimen showing extensive sarcoid, bullous and abscess involvement of the lungs.

On December 3, 1954, there was sudden onset of right chest pain due to a spontaneous pneumothorax (figure 6). At first, aspiration of the air relieved the dyspnea, but tube suction was necessary later. Sputum cultures again contained many bacteria and *M. albicans*. Fever, dyspnea, cyanosis, increased respiratory acidosis due to accumulation of CO_2 and somnolence developed. Because of the patient's critical condition, cortisone, 25 mg. four times a day, was given, and this resulted in lessening of the fever, a sense of well being, and general improvement. However, cough, expectoration, dyspnea and respiratory acidosis continued, and on December 17, 1954, there was another sudden right spontaneous pneumothorax, requiring tube drainage. Subsequently, purulent infection of the pleura occurred and a bronchopleural cutaneous fistula developed. Death occurred on February 14, 1955.

Postmortem Examination: Gross Findings:* A 15 mm. pleurocutaneous fistula was present in the right lateral chest wall. The pleura was partially obliterated by

* Performed by Dr. Nelson G. Holmquist.

fibrous adhesions which bound the partially collapsed lung to the thoracic wall. The adhesions and collapsed lung were covered by a layer of light green purulent fluid. Several colonies of fungus composed of the fine gray mycelia were grown out on the surface of the purulent fluid. The left pleural cavity was obliterated by fibrous adhesions.

The lungs (figure 7) contained many nodular lesions with numerous thin-walled abscesses which were full of pale green purulent material. The largest abscess measured 5 cm. in diameter and was located in the lateral portion of the left upper lobe. The hilar mediastinal and parapancreatic lymph nodes were enlarged up to 4 cm. in diameter, and on section were firm and a gray-yellow in color. The rest of the organs, including the heart and brain, were normal.

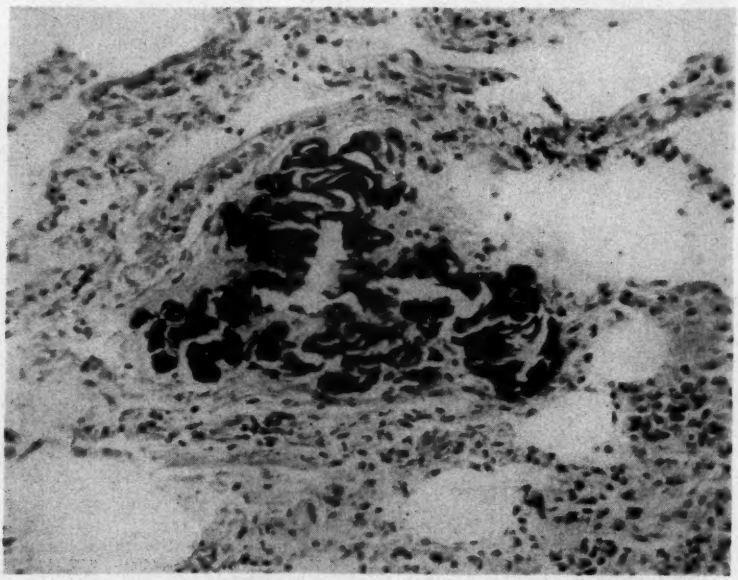

FIG. 8. *Case 2.* Photomicrographs of the lungs. A. (Hematoxylin and eosin stain ×200) A large calcified nodule is seen in center; elsewhere there is widespread emphysema; the alveoli are filled with granulomatous epithelial and giant cells.

Microscopic Findings: All sections of the lung contained granulomata consisting of aggregations of epithelioid cells and multinucleated giant cells. Calcifications (figure 8A) were everywhere, within alveolar walls and granulomata. In addition, there were many lung abscesses, each surrounded by zones of consolidation containing necrotic tissue, polymorphonuclear leukocytes, and thin walls of granulation tissue with myriads of spores, mycelia and colonies of cocci. The spores (figure 8B) varied from 3 to 6 micra in diameter; the mycelia were about 6 micra in diameter and were branched and segmented. Sections stained for acid-fast bacilli were negative.

Sections of hilar and parapancreatic lymph nodes revealed almost complete replacement of the lymphoid tissue by confluent nodules of collagenous tissue and numerous small calcified bodies. Occasionally, a small granuloma with a multinuclear giant cell was seen. No acid-fast bacilli were found.

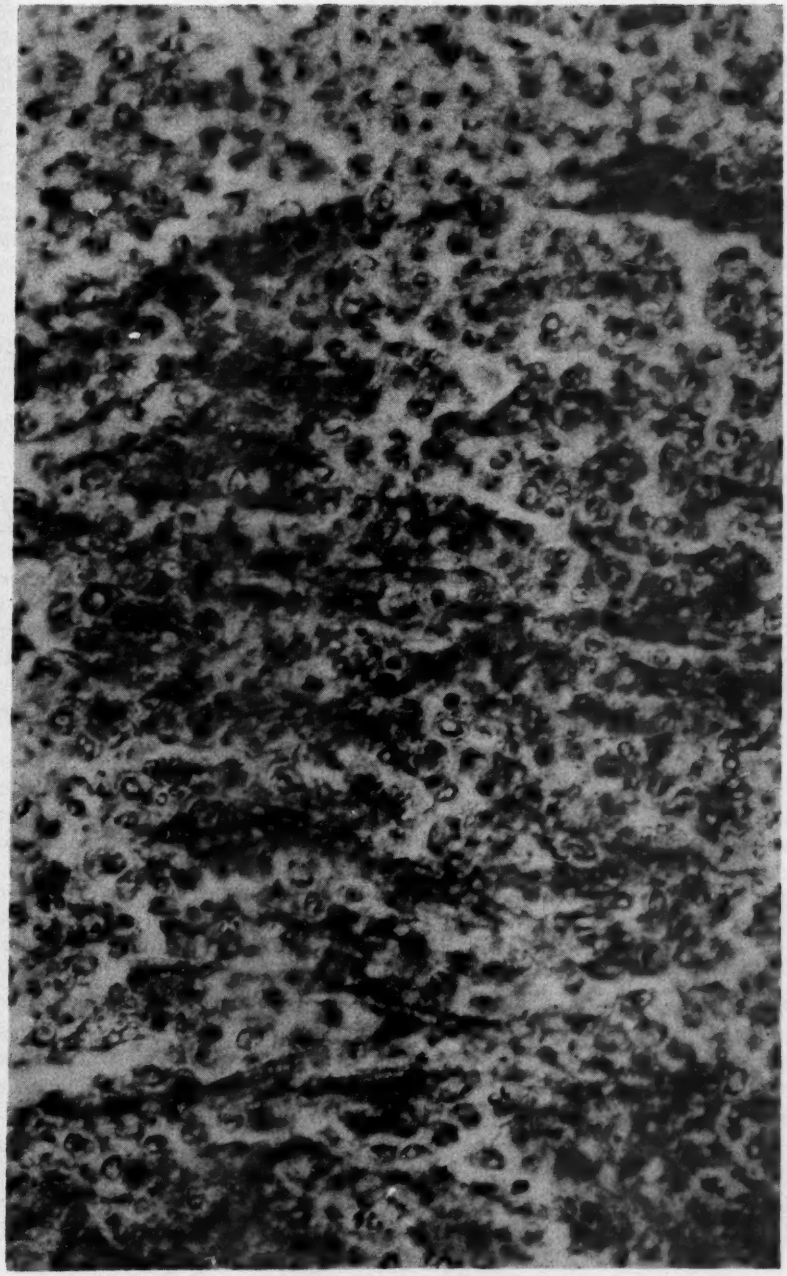

FIG. 8. B. (Hematoxylin and eosin stain × 600) Myriads of yeast spores in pulmonary abscess.

Bacterial Examination: Lung culture yielded *Escherichia coli, Proteus rettgeri,* gamma streptococcus, *Aspergillus glaucus,* and *Monilia albicans. Final Diagnosis:* Boeck's sarcoid of hilar, mediastinal and parapancreatic lymph nodes, skin and lung. Multiple abscesses of lung, emphysema and a bronchopleural fistula containing mixed flora of fungi and bacteria.

Discussion

Sarcoidosis is a generalized granulomatous disease of unknown etiology. The diagnosis usually depends upon the histologic demonstration of the lesion on biopsy or necropsy, although the disease can often be suspected on clinical grounds. A voluminous literature concerning all the various aspects of the disease has accumulated and is included in recent reviews.[9-11]

Pulmonary manifestations of sarcoidosis are a prominent feature of the disease and include mediastinal and hilar lymphadenopathy, as well as many types of pulmonary involvement. Extensive pulmonary fibrosis may lead to pulmonary hypertension and cause heart failure due to cor pulmonale.[7, 8, 10, 12, 13] In addition, obliterative arteritis of the pulmonary vessels has been noted.[14-16] The presence of ectatic bronchi and blebs simulating pulmonary cavities has also been described.[14, 16, 17, 18]

Both patients reported here had widespread pulmonary fibrosis and emphysema. Case 1 had pulmonary hypertension, but information regarding the presence of right ventricle enlargement at autopsy was not obtained. Case 2 showed no evidence of sarcoidosis of the heart or of right ventricular hypertrophy. In both patients, widespread bilateral bullous emphysema (figures 1, 5, 6) was present. In addition, the second patient had multiple spontaneous pneumothoraces which required suction drainage and were complicated by the development of a bronchocutaneous fistula. Respiratory insufficiency was a prominent feature of the disease in both cases; respiratory failure in case 2 was critical.

A recent summary of the pulmonary complications of ACTH and cortisone from the New York Hospital did not include fungus infection.[19] Both patients received antibiotic and hormonal therapy, although the amount of hormone therapy prescribed toward the end of the illness in case 1 is unknown. While the yeast infection may have been incidental, the evidence from the literature appears to support the causal relationship between the development of virulent disseminated fungi and antibiotic and hormonal therapy.[1, 3-5] Fungus infection in case 1 was not suspected until meningitis due to nocardiosis developed. Although complete information regarding the autopsy findings in the lungs in case 1 is not available, it appears likely that the yeast infection was also present in the pulmonary tissues. In case 2, monilia was cultured from the sputum on many occasions. Because of its frequent appearance in sputa, it was not recognized as being significant until necropsy disclosed the mold in the pulmonary and pleural tissues.

It would appear that patients with progressive pulmonary sarcoidosis who develop pulmonary insufficiency are prone to have pulmonary infections. Antibiotic therapy is effective for a long time and alleviates the bacterial infections. Hormonal therapy apparently results in amelioration of symptoms caused by

infection and pulmonary insufficiency. Eventually, antibiotics alone or in combination with hormones set the stage for the development of disseminated virulent fungus disease.

The development of antibiotics with antifungal properties may prove of assistance where long term antibiotic and hormonal therapy is required.[20-22]

Summary and Conclusions

Fatal fungus infection in two advanced cases of sarcoidosis is reported. Widespread pulmonary sarcoid disease resulted in severe pulmonary insufficiency and infection. Antibiotic and cortisone therapies were followed by temporary improvement but were apparently responsible for the development of disseminated virulent fungus disease.

Acknowledgment

Thanks are due to the Department of Pathology for permission to report the postmortem findings in case 2.

Addendum

Since this paper was submitted for publication, there have been several new reports in the literature describing the development of fungus disease following antibiotic and steroid therapy. Torack [23] recently reported a large series.

Summario in Interlingua

Reportos de mortal infectiones fungal appare plus frequentemente in le litteratura. Isto es attribuibile al crescente incidentia e virulentia de fungos in consequentia del suppression de bacterios per antibioticos e alterationes del reactiones in le organismo hospite sub le influentia de therapia hormonal (ACTH e cortisona). Illo es etiam attribuibile, in parte, al meliorate methodos de diagnose fungal providite per le moderne methodos de inoculation cultural e animal e etiam per nove technicas histopathologic. Disseminate infection fungal ha etiam essite reportate como complication de morbos del typo de anemia aplastic, lymphoma, leucemia, diabete, tuberculose, e cancere.

Duo patientes con sever insufficientia pulmonar causate per sarcoidosis pulmonar experientiava un melioration temporari de lor dyspnea gratias al therapia con antibioticos e cortisona. In le un, abscessos cerebral e meningitis causate per *Nocardia asteroides* se disveloppava. Le secunde habeva repetite pneumothoraces spontanee como effecto de rupturate bullas emphysematose, associate con le disveloppamento de un fistula bronchocutanee e febre. Ben que *Monilia albicans* esseva trovate in un cultura de sputo, illo esseva considerate como un contaminante. Al necropsia—a parte extense sarcoidosis del pulmones e nodos lymphatic—multiple abscessos pulmonar esseva trovate le quales includeva in lor tenue parietes myriades de fungos e coccos. Colonias de fungos esseva etiam trovate in le canal del fistula bronchocutanee.

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LUNG ABSCESS COMPLICATING A HEALED OPEN TUBERCULOUS CAVITY*

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This case is being presented to call attention to the unusual response of a healed open tuberculous cavity complicated by a coincident lung abscess. The unusual character of healed tuberculous lesions has been widely described in current literature. As a result of therapy with the new chemotherapeutic agents, lesions that formerly terminated fatally are now being healed or arrested. As more patients are released from sanatorium care and are exposed to the bacterial vicissitudes of the general population, complications such as this may become more prevalent.

Case Report

A 33 year old Negro male, in October, 1951, while working in an industrial plant, first noted onset of generalized malaise, weakness, intermittent elevation in temperature, anorexia, night sweats, exertional dyspnea and a 15 pound weight loss. He developed a slightly productive cough, yielding a half ounce of sputum daily. A chest film taken at the Philadelphia General Hospital revealed a large left apical cavity. Sputum was positive for acid-fast bacilli. He was instructed to remain in bed while awaiting hospitalization. Immediate hospitalization could not be accomplished. Chemotherapy was begun in January, 1952, with streptomycin, 1 gm. twice weekly, and para-aminosalicylic acid, 12 to 16 gm. daily. He failed to gain weight; cough and expectoration persisted, and dull chest pain was noted in the lower left lateral axilla with cough and respiration.

On the patient's admission to the Jefferson Medical College, White Haven, Pennsylvania, May 14, 1952, a negative family and personal history was obtained. His occupation had been that of a cook. No unusual industrial exposures had occurred. Chest X-ray in 1943, while he was in the Army, had been normal. The patient weighed 124 pounds (former weight, 155 pounds). He was raising 100 to 200 c.c. of yellow, mucoid sputum.

The pertinent physical findings on admission were limited to the chest. *Right lung:* Normal findings on percussion. On auscultation: multiple crepitant inspiratory râles, occasionally a few wheezes over the upper two thirds anteriorly and posteriorly. Expiratory grunting sounds over the midchest anteriorly. *Left lung:* Tympany over the apical area. Flatness over the entire anterior chest except the outermost lateral lower portion. Slight dullness over upper two thirds posteriorly; impaired excursions at base. Diminished vocal fremitus over anterior chest and over upper two thirds posteriorly. On auscultation: diminished breath sounds with multiple crepitant and sonorous râles and a few wheezes over anterior chest and posterior upper two thirds. Increased whispered voice transmission over the same areas.

Laboratory examination revealed positive sputum throughout the period from October, 1952, until January, 1953. Ten later sputum tests from January to March, 1953, were negative for tubercle bacilli. Sedimentation rate (Wintrobe) was 10 mm. in 1 hour; hemoglobin, 91 gm.%; red count, 4,500,000; white count, 5,000, with lymphocytes, 44%; monocytes, 2%; eosinophils, 1%; basophils, 1%. Urinalysis showed a specific gravity of 1.014; reaction, acid; albumin, negative; sugar, negative.

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No formed elements were noted. A diagnosis of far advanced pulmonary tuberculosis with cavitation of the left apex was made.

The initial chest film (figure 1, May 5, 1952) reveals evidence of an acute caseous pneumonic consolidation involving the whole left lung. There is a tendency toward left mediastinal shift. Several hazy areas of rarefaction, irregular in outline and indistinct in detail, are noted at the apical and basal segments of the lung. The left diaphragm is elevated. The right lung appears intact.

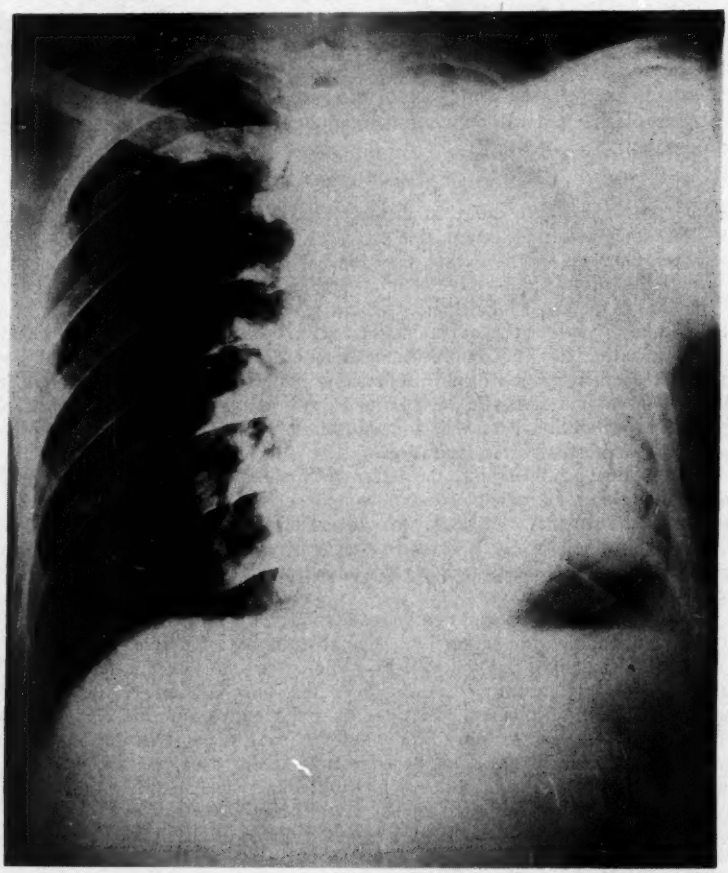

FIG. 1. Dense pneumonic consolidation of left lung.

Figure 2 (May 20, 1952) represents a tomogram taken at the 11 cm. posterior level. This film demonstrates distinct evidence of multiple areas of cavitation in the left apex.

A chest film dated July 17, 1952 shows essentially the same process involving the left lung, and some suggestive infiltration in the right lung.

The patient was bronchoscoped on July 22, 1952, at which time a markedly inflamed bronchial mucosa was noted. He was again bronchoscoped on March 17,

1953. The trachea was normal. The carina was pulled slightly to the left, and the left main stem bronchus was entirely free of any endobronchial disease.

Figure 3 (chest film dated September 14, 1952) reveals the far advanced tuberculous process in the left lung. There was also definite evidence at this time of contralateral spread, with infiltration involving the upper half of the right lung.

A chest film dated October 20, 1952, for the first time revealed some improvement. The left base was better aerated, the consolidation diminished, and in scattered areas lung tissue could be visualized. The exudative process in the right lung was also clearing.

Figure 4 (March 30, 1953) shows progressive improvement. Fibrosis with definite mediastinal shift is seen. The left main bronchus is identified, and is seen

FIG. 2. Tomogram taken at 11 cm. posterior level, evidencing areas of cavitation in the left apex.

pulled to the left as well as the trachea. The entire left hemithorax is contracted. The left lung is now well aerated. Scattered areas of residual disease persist. The right lung appears free of disease. There is a suggestion of bullous emphysema or cavity formation at the left apex, associated with fibrosis and retraction of the upper lobe in this area. This film was the last hospital film prior to his release, and represents essentially the same picture as on his admission later to the U. S. Penitentiary at Lewisburg, Pennsylvania.

A complete record of hospitalization therapy reveals that the patient received 1 gm. of streptomycin twice weekly, from May 15, 1952, until March 28, 1953, for a total of 90 gm. Para-aminosalicylic acid was given from May 14, 1952, until March 28, 1953, for a total of 3,192 gm. Isoniazid was given from July 21, 1952, until August 28, 1953, for a total of 1,338 tablets of 50 mg. each. The patient was

released from the Barton Memorial Division on March 28, 1953, and was followed for a short period in the out-patient department.

He did well and was asymptomatic from the period beginning in March, 1953, until his arrival at the Federal Penitentiary at Lewisburg, Pennsylvania, in May, 1955. He had lost no weight, was afebrile, and had no dyspnea at rest, chest pain or cough.

Figure 5 (chest x-ray taken May 16, 1955, at the U. S. Penitentiary Hospital, Lewisburg, Pennsylvania) reveals the fibrotic left lung, an elevated left diaphragm, and apical pleural thickening. The bullous area is noted as before, and increased fibrovascular markings are noted in the region of the left interlobar fissure. Pleural

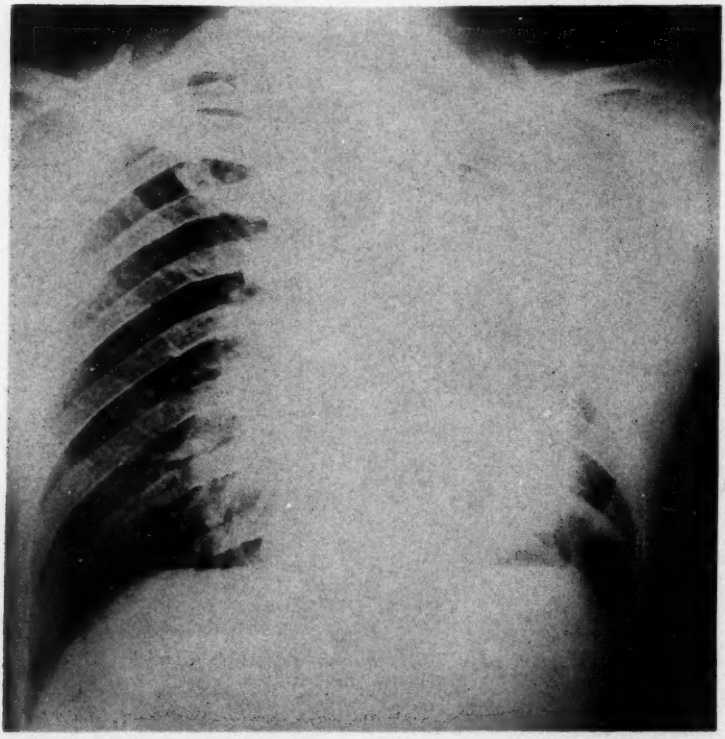

FIG. 3. Evidence of contralateral spread involving upper half of right lung.

thickening and fibrous scarrings are noted at the left base. The sedimentation rate (Wintrobe) at that time was 11 mm. in 1 hour. Examination of the urine was negative. The hemoglobin and white count were normal. Gastric washings were negative for acid-fast bacilli on smear, culture and guinea pig inoculation.

The patient felt well until Saturday, August 6, 1955, when he suddenly developed malaise, generalized chilly sensations and fever after having been caught in a sudden summer rain. Forty-eight hours later he noted severe left lower anterior chest pain on deep inspiration. This pain was relieved with sudden onset of copious productive sputum amounting to 3 to 4 ounces in a 24 hour period. The sputum had

no blood, had a somewhat foul odor, and was definitely layered and greenish and mucopurulent in character. A temperature of 104° F. and pulse of 100 were recorded.

At this time the patient weighed 162 pounds. Decreased amplitude of respiratory excursions was noted on the left. There was dullness over the upper half of the left chest posteriorly. There was diminished tactile fremitus. There was evidence of egophony over the posterior upper one third of the left lung at the inferior

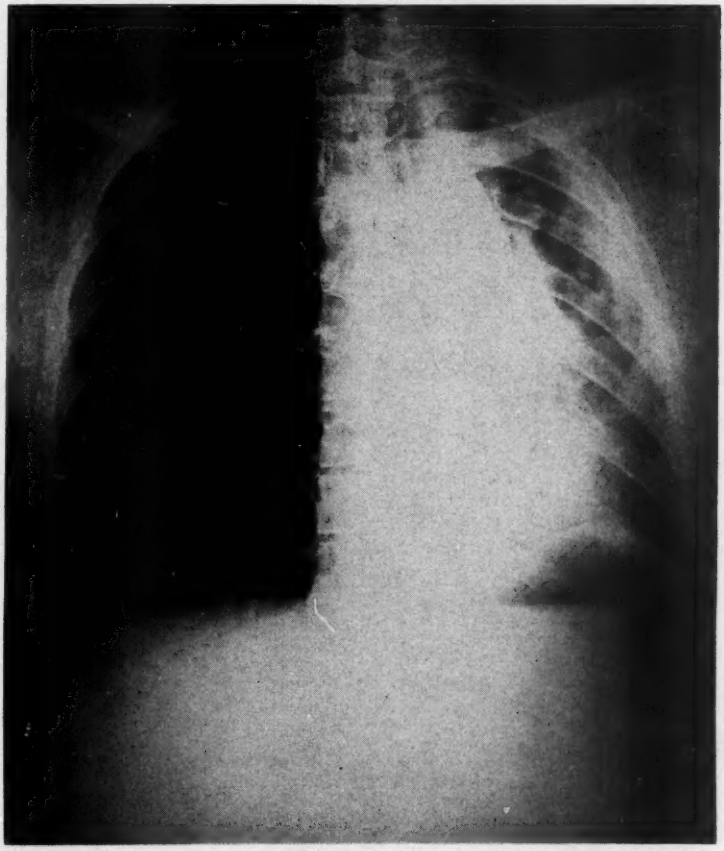

FIG. 4. Evidence of marked improvement. Mediastinal shift to left and elevation of left diaphragm are marked. Partial clearing of left lung.

scapular angle. There was a diffuse bronchial wheeze on both inspiration and expiration, but more pronounced on expiration. There were diffuse consonating râles throughout the entire area. No evidence of tympany or increased resonance could be found at this time. The heart was shifted, and P_2 was accentuated. No edema, cyanosis or clubbing was noted.

Figure 6 (chest x-ray taken August 9, 1955) revealed a giant cavity involving

almost the entire left upper lobe. A fluid level was seen in close proximity to the long fissure. Consolidation in the left lower lung was noted. A right lateral recumbent film demonstrated the extent of the fluid level and size of the cavity in the left upper lobe. The thickened interlobar fissure was well demonstrated.

Blood cultures were negative. Blood count revealed 1,950 white blood cells, with 70% neutrophils, 22% lymphocytes, 1% monocytes and 2% eosinophils. The

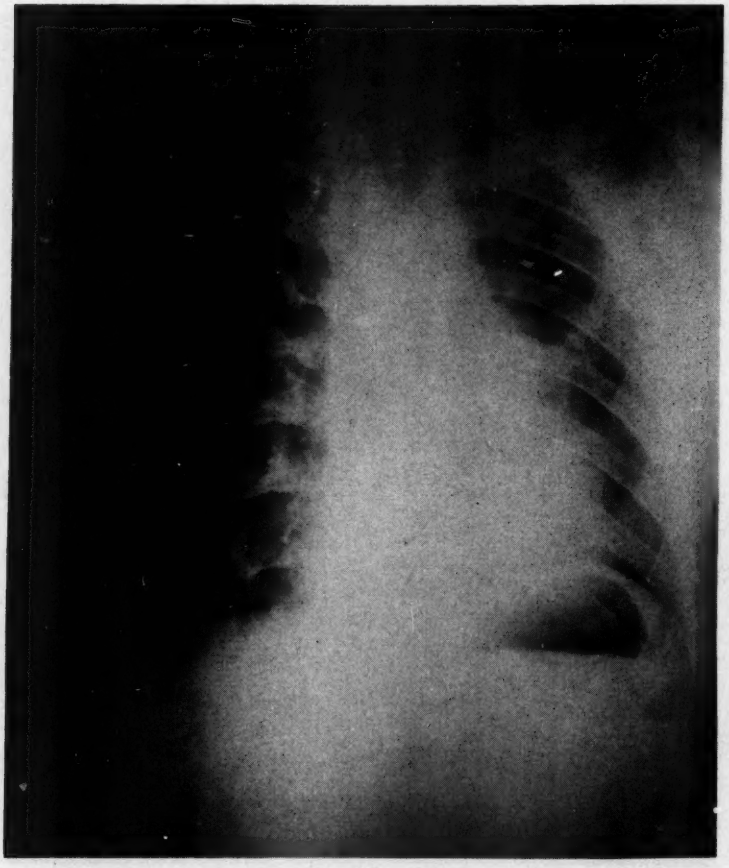

FIG. 5. Further improvement between March 1953 and May 1955.

hemoglobin was 12 gm.%; sedimentation rate (Wintrobe) 51 mm. in 1 hour; hematocrit, 41%. The urine was negative. Sputum cultures revealed many gram-positive cocci in pairs and chains and some gram-negative cocci. On subculture the following organisms were identified: (1) *Bacillus pyocyaneus;* (2) many hemolytic staphylococci, coagulase-positive; (3) many Neisseriae; (4) some *Streptococcus viridans.* The sputum was negative for acid-fast bacilli on smear, culture and guinea pig inoculation. The organisms were then studied for sensitivity and were found

most sensitive to penicillin and oxytetracycline. The patient was placed on oxytetracycline every six hours after a priming dose of 1 gm. before the results of antibiotic sensitivity were known. Within 24 hours the temperature had receded to 101° F., and in 48 hours had dropped to normal. The sputum immediately diminished in volume and became mucoid in character. By the fifth day no further sputum was being raised. Within one week the patient was asymptomatic.

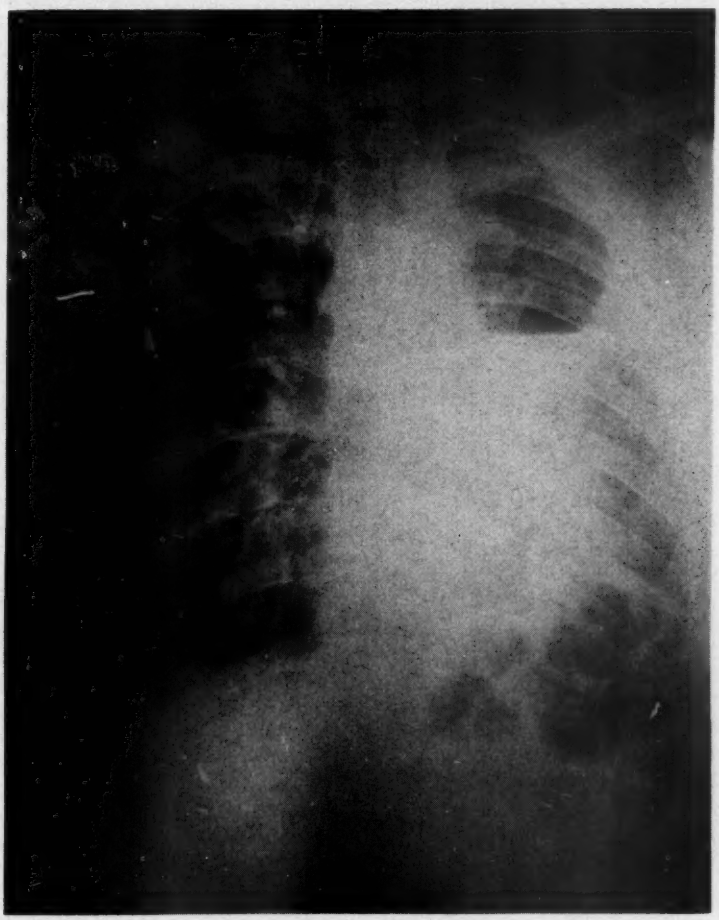

FIG. 6. Development of lung abscess cavity with fluid level.

The impressions on admission were either bronchopleural fistula with pyopneumothorax involving the left upper lobe, or giant cavity involving the left upper lobe almost in its entirety.

The patient made a remarkable response to the chemotherapeutic agents. A posterior-anterior view (taken on August 11, 1955) revealed the same process un-

changed. Figure 7 (August 23, 1955) 13 days after the onset of the acute pneumonic episode, no longer demonstrated the cavity. The picture was that of the admission film of May 16, 1955 (figure 5), and essentially similar to that of March 30, 1953, the discharge film from the White Haven Sanatorium. The radiolucent area at the left apex had returned to its former size and configuration.

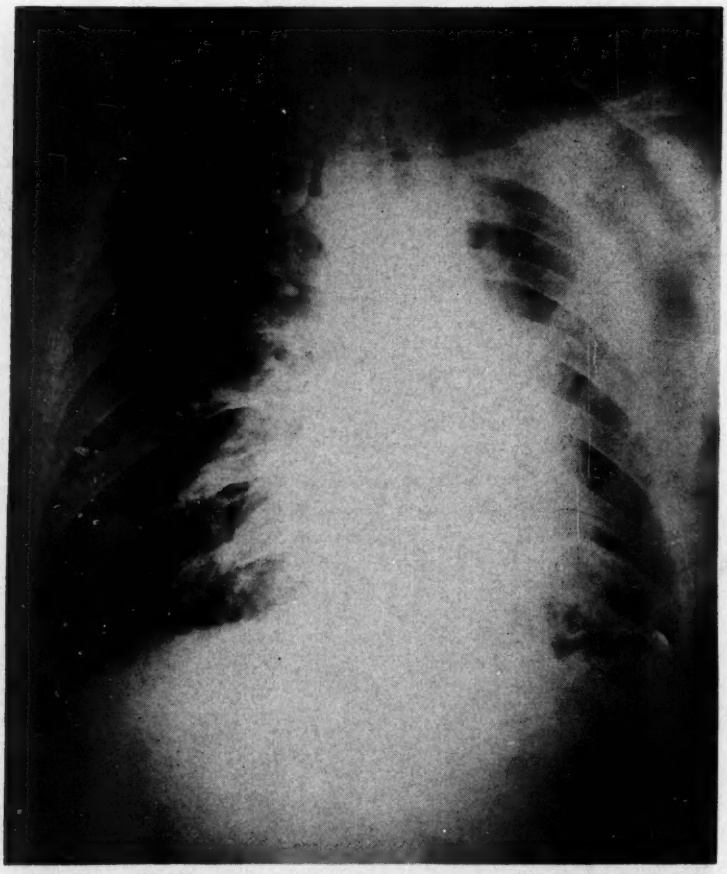

FIG. 7. Taken 13 days after figure 6, this film no longer shows the large cavity. The condition has reverted to that shown in figure 5.

The patient was then transferred to The Medical Center for Federal Prisoners at Springfield, Missouri, where he was observed on the tuberculosis service. He gained weight, and there was no further cough or chest pain. Cultures and bronchial lavages were negative for acid-fast bacilli. The patient was evaluated for surgery. It was felt that it would be difficult or impossible to remove only the left upper lobe, since the destructive disease process of 1952 appeared to have involved the interlobar pleura. Thus it would not be possible to separate the lobes and pneu-

monectomy would be necessary. The left lower lobe had evidence of considerable destroyed tissue, scarring and encapsulated nodular tuberculous lesions. Pneumonectomy would thus appear to be the treatment of choice. However, because the patient had had considerable disease of the right upper lung in 1952, it was felt he would not be a good candidate for left pneumonectomy and there would be the risk of his becoming a respiratory cripple even if no exacerbation of the disease in the right lung occurred.

Auerbach [1] has recently described cavity healing in pulmonary tuberculosis after prolonged chemotherapy. Closed healing occurs with obliteration of the cavity, with inspissation of its contents, or replacement by a radial scar. Open healing, on the other hand, permits the cavity to remain. The wall is composed of dense connective tissue from which all elements of specificity have often disappeared. Occasionally it is partially or completely lined by a layer of epithelium, usually squamous. In open healing the necrotic lining is either desquamated or converted into dense hyalinized connective tissue. The bronchi opening into the cavity are widely patent, lined by intact columnar epithelium, and show no evidence of tuberculosis. Reëpithelization at the bronchocavitary junction disrupts the check valve mechanism, and prevents obliteration of the bronchial lumen and permanent closure of the cavity without distention. We feel that this was the type of healing that occurred in this case. The large upper lobe cavity healed in an open manner, with a thin wall, and so was not clearly visible.

Tuberculous lesions under chemotherapy heal with rapid clearing of inflammatory exudate and with less scarring and emphysema.

This case represents an unusually good response to therapy in an advanced tuberculous process. The clinical validity of the absence of viable acid-fast bacilli must depend not only on negative routine laboratory examination but also on the rapid healing of the giant cavity without evidence of new tuberculous activity.

The history of a sudden pneumonic episode in August, 1955, occurring with the production of purulent sputum within 48 hours, suggested the development of a lung abscess. The abscess was able to develop rapidly at the site of a preexisting healed open tuberculous cavity. The presence of the cavity was revealed by the fluid level which developed as the draining bronchus became plugged with fibrinous exudate. The same process occurs in infected lung cysts.

Amberson [2] has noted that the first favorable responses to chemotherapy are subsidence of acute inflammation, alleviation of signs of general toxemia, diminished exudation and halting of the extension of lesions demonstrated by x-ray. This process may not be demonstrable for several months, as was the case with our patient.

Although necrosis may take place in any part of an exudative lesion, the process is prevented in areas where resolution intervenes. While resolution occurs at the periphery, the necrotic centers may continue to undergo liquefaction and excavation. This is most pronounced in acute cases, in which extensive caseation has occurred before starting therapy. In other cases, chemotherapy arrests sloughing and the caseous matter may become inspissated.

After evacuation of its contents the cavity shrinks, aided by resolution of bronchial mucosal inflammation. Residual air and purulent exudates are re-

leased. The walls of some cavities consist of "clean" fibrous tissue, with bronchial epithelial overgrowth. Elements of tuberculosis persist in most.

Hobby et al.[3] noted that tubercle bacilli may remain viable within necrotic foci. Prolonged incubation was necessary for their detection after long and repeated courses of therapy. In this case no tuberculous reactivation was demonstrated clinically.

No correlation between the presence of viable tubercle bacilli in tuberculous lesions and duration of chemotherapy, drug regimens used, duration of preoperative period, noninfectiousness or anatomic nature of the lesion could be demonstrated by Auerbach.[4]

Medlar [5] has noted that tuberculous foci in the apical and posterior portions of various lobes often become caseous and act as active abscesses that never heal completely. They harbor constant danger of liquefaction and sloughing of their necrotic centers into a connecting bronchus.

Muschenheim [6] in his recent discussion of therapy stated that persistent small cavities and repeated negative cultures make resection debatable. It is often difficult to distinguish true cavities from emphysematous bullae. Residual closed lesions, filled in cavities and other necrotic residues are not often resected. One can afford to wait as long as there are no disastrous sudden spreads. There is often decreased mortality with chemotherapy, and it is possible to avoid respiratory cripples secondary to extensive surgery. Destroyed segments are often less than may be anticipated at pathologic examination. If there is no positive sputum, waiting is advised. Even with positive sputum and cavitation, antimicrobial therapy and possible reversible collapse procedures are worth while. Trial with pneumothorax might be useful except for unusually large or obviously fibrous-walled cavities, and except in the presence of a stenotic bronchus.

Judged by these findings, inspissated cavities with communicating bronchi are potentially dangerous in a high percentage of cases after prolonged chemotherapy or the regimens used universally today.

With or without therapy, it is often impossible to distinguish between necrotic lesions and filled-in cavities, although open cavities often, but not always, have less exudate. Although walled-off necrotic lesions have little effect on contiguous lung tissue, there are four hazards: (1) the dead tuberculous tissue is often difficult to dispose of; (2) the bacillary content remains and, although often nonviable to animals, may still be a source of relapse; (3) necrotic lesions tend to liquefy and slough; (4) vulnerable points of necrotic lesions are often associated with patent connecting bronchi.

Sze et al.[7] noted these indications for resection: (1) persistent cavitary disease; (2) destroyed lung or lobes; (3) thoracoplasty failure; (4) residual caseonecrotic disease; (5) bronchostenosis; (6) diagnostic problems, and (7) bronchiectasis.

Unfortunately, at this patient's stage resection has been ruled out. The left upper lobe, however, remains a site of future potential difficulty.

In summary, a case of lung abscess complica ing a healed open tuberculous cavity has been presented. This case is remarkable in that the complicating lung abscess apparently did not reactivate the tuberculosis.

ACKNOWLEDGMENT

The author wishes to express his indebtedness to Dr. John S. Packard, Medical Director of Devitts Camp, Allenwood, Pennsylvania, and to Dr. Charles Laubach, of The Foss Clinic, Geisinger Memorial Hospital, Danville, Pennsylvania.

Photography was made possible by Mr. T. Y. Lawrence, of the United States Penitentiary at Lewisburg, Pennsylvania.

SUMMARIO IN INTERLINGUA

Es presentate un caso de resanate cavitate tuberculotic aperte, in un juvene masculo negre, complicate per pneumonia e un abscesso pulmonar que non reactivava le tuberculose pulmonar.

Un episodio acute de caseose pneumonia tuberculotic, afficiente le complete pulmon sinistre in maio 1952, respondeva a 1 g de streptomycina duo vices per septtimana e acido para-aminosalicylic e isoniazido in dosage usual durante un periodo de inter 9 e 13 menses. Tamen, un grande cavitate residue al apice sinistre esseva formate. Le examine del sputo esseva negative pro bacillos tubercular in frottis e cultura a partir de januario 1953. Le patiente se trovava ben usque augusto 1955 quando—post su exposition a un pluvia de estate—ille disveloppava un episodio de pneumonia acute con le formation de un gigante cavitate in le apice sinistre. In despecto de copiose quantitates de sputo, nulle signos de reactivation tuberculotic esseva trovate. Le responsa a oxytetracyclina esseva dramatic, e intra un septimana le patiente esseva asymptomatic, e le roentgenogramma habeva retornate al previe configuration basal.

Es postulate que resanation aperte habeva occurrite sin clausion del cavitate. Ben que iste area curre un risco constante de activation, un apparente episodio pneumonic occurreva intercurrentemente, producente un grande cavitate in le lobo superior sin reactivar le tuberculose pulmonar.

Il es a expectar que iste typo de complication va esser incontrate plus frequentemente, al mesura que sanatorios pro patientes de tuberculose pulmonar es reimplaciate per le regime de tractamento visitante.

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LISTERIA MONOCYTOGENES MENINGITIS *

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LISTERIA *monocytogenes* was described as a new species in 1926 by Murray et al.,[1] and human infection caused by this microörganism was first reported in 1936 by Burn.[2, 3] Several recent papers have amply reviewed the literature.[4, 5, 6, 7] *L. monocytogenes,* although not very often shown to be the cause of acute meningitis, may be mistaken for a contaminant "hemolytic diphtheroid" unless particular diagnostic criteria are applied. Since the etiologic importance of this organism can therefore be easily overlooked, it seems desirable to record one additional case.

CASE REPORT

The patient was a 62 year old woman whose past history included moderate hypertension of about 10 years' duration, and what was said to have been a subarachnoid hemorrhage six years before the present illness. There had been no known exposure to infectious disease in the recent past. During the day prior to admission the patient noted lassitude and excessive fatigue, and had a chill in the evening. She was awakened later that night by severe headache, and by morning there was also severe pain extending down the back to the buttocks. The temperature was 101° F. orally. She was examined at this time by one of us (H. S.) and found to have marked stiffness of the neck, a blood pressure of 180/80 mm. of Hg, and a grade II systolic murmur at the apex. Skin, nose, throat and lungs were not remarkable. A white blood cell count was 13,600 per cubic millimeter, with 88% polymorphonuclears. The patient was brought to the hospital by ambulance. On admission the temperature was 104° F. rectally. There were continued marked nuchal rigidity and a fine tremor of both outstretched hands. There were no localizing neurologic findings, and no petechiae. The initial lumbar puncture revealed "ground glass" spinal fluid, with 1,120 leukocytes per cubic millimeter, 90% of which were polymorphonuclears. An organism characterized as a "diphtheroid," as well as *Micrococcus tetragenus,* was isolated from the first spinal fluid culture. The course of the patient's illness, laboratory data and therapy are summarized in the figure 1.

It was felt that both the "diphtheroid" and the micrococcus represented contaminants, but because of the preponderance of polymorphonuclear leukocytes in the spinal fluid the possibility of bacterial meningitis due to some unrecognized organism seemed real. No intrathecal antibiotic was administered, but penicillin was started intramuscularly, and both sulfadiazine and chloramphenicol orally. There was a gradual fall in fever and marked symptomatic improvement occurred with complete disappearance of meningeal signs. By the tenth day the temperature was normal, though the spinal fluid continued to show a lymphocytic reaction. At this point it was considered most likely that the meningitis had been of viral origin, and antibiotic therapy was discontinued on the ninth day. From the tenth to the twentieth days the temperature did not exceed 100° F. rectally, and the patient continued to feel better. On the twenty-first day meningeal signs and fever recurred. The total

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spinal fluid leukocyte count had risen to 1,950 per cubic millimeter, with a marked polymorphonuclear reaction, indicating a relapse of meningitis. "Diphtheroids" were again reported in cultures of the spinal fluid made on the twenty-first and twenty-second days, before the resumption of antibiotic therapy. When this organism proved to be lethal for mice, the suggestion was made by Dr. H. M. Rose that it might be *Listeria monocytogenes,* a diagnosis established by subsequent studies.

Treatment with penicillin, chloramphenicol and streptomycin was instituted, and the patient made a prompt response, as shown by the fall in temperature, rapid symptomatic improvement, and consistently sterile spinal fluid. A mild pleocytosis continued, but by the thirty-fifth day—that is, two weeks after the recurrence of meningitis—the spinal fluid contained only 24 lymphocytes per cubic millimeter, and was otherwise normal. The patient was afebrile from the fortieth day on, and con-

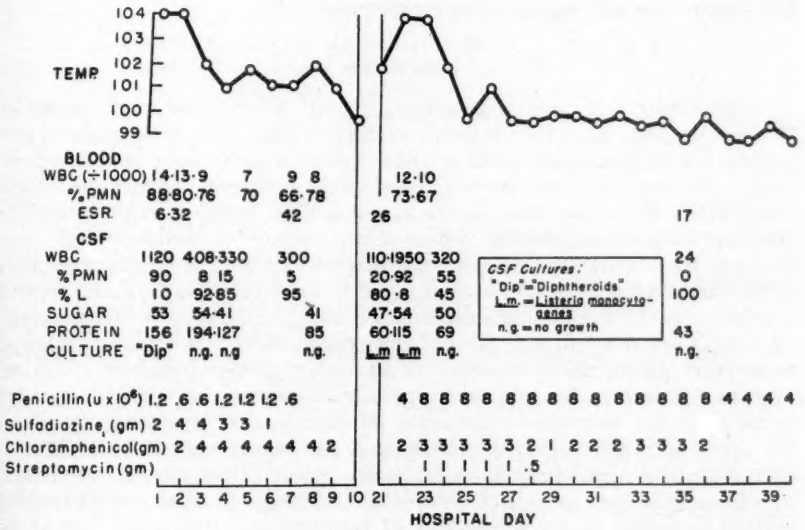

FIG. 1. Course of disease, laboratory data and therapy.

valescence was uneventful. Six months after discharge she was reported to be in good health.

BACTERIOLOGY

Blood cultures taken on admission and on the twenty-seventh day, at the time of recurrence of meningitis, remained sterile. The microörganism isolated from the spinal fluid on the twenty-first and twenty-second days had the following characteristics: It was a Gram-positive rod, resembling diphtheroids morphologically, and was actively motile. It produced beta hemolysis on sheep blood agar, and was lethal to adult mice 18 hours after intraperitoneal inoculation. Galactose, dextrose, salicin and maltose were fermented without gas production; sucrose, lactose and mannitol were not fermented. Hydrogen sulfide was not produced, indole was not formed from tryptophan, and urea was not hydrolyzed. The patient's serum taken on three occasions (the tenth, thirtieth and fiftieth

days after onset of illness) failed to agglutinate the microörganism even in low dilution. It was, however, agglutinated to moderate titer by several normal sera selected at random. It was found to be sensitive in vitro to 0.3 unit of penicillin per milliliter, and 5 μg. of streptomycin per milliliter. It was also found to be sensitive, when tested by the disc method, to Terramycin, bacitracin, Achromycin, erythromycin and chloramphenicol. A subculture submitted to the Communicable Disease Center, Chamblee, Georgia, was identified as *L. monocytogenes*. The morphologic similarity of this isolate to ordinary diphtheroids, usually considered to be contaminants, supported the view that the microörganism isolated from the spinal fluid at the beginning of the patient's illness, although reported as a "diphtheroid," had actually been the causative agent subsequently correctly identified. The micrococcus grown from the initial spinal fluid culture was still regarded as a contaminant.

Comment

Approximately 40 cases of meningitis, proved or presumed to be caused by *L. monocytogenes,* have been reported to date. These have been sporadic, and in none has the source of infection or the portal of entry been established, although this organism is a fairly common animal pathogen. Before the advent of antibiotics the human case fatality rate was high (68% or more[8]). While sulfonamides have proved to be of little value, a number of antibiotics have been shown to be effective, both in vitro and in vivo. Strains of *L. monocytogenes* isolated from human cases have been found to be sensitive to penicillin as well as to most of the other antibiotics in common use. In the present case, although the organism was sensitive to all antibiotics tested, there was only a slow fall in temperature during the first episode of meningitis, despite treatment. The relapse may have been brought on by premature cessation of antibiotic therapy on the ninth day, since the nature of the infection was not clear until the causative agent was identified on the twenty-first and twenty-second days. It is of interest that the spinal fluid showed a predominance of polymorphonuclear leukocytes early in each episode of meningitis, changing with clinical improvement on both occasions to a predominance of lymphocytes. The sugar was at no time greatly depressed. The failure of the patient's serum to agglutinate the strain of *L. monocytogenes* isolated from the spinal fluid is not inconsistent with the etiologic diagnosis, since specific agglutinins are not regularly present in these infections. Indeed, the capacity of normal sera to agglutinate *L. monocytogenes,* as in the present instance, opens the specificity of such agglutinins to suspicion unless they are present in the extremely high titer or show a significant rise during the course of illness.[9]

Summary

A case of meningitis in an adult due to *L. monocytogenes* is reported. Recovery was complete following the use of penicillin, chloramphenicol and streptomycin. The possibility is reëmphasized that *L. monocytogenes* may be mistaken for "contaminant" diphtheroids and therefore not recognized as a cause of human disease.

SUMMARIO IN INTERLINGUA

Es reportate un caso de meningitis in un patiente adulte, causate per *Listeria monocytogenes*. Le fonte del infection non esseva identificate. Nulle agglutininas specific appareva durante le curso del infection, ben que le organismo causative esseva obtenite ab le fluido cerebrospinal in duo essayos ante le institution del therapia antibiotic. Le identification del micro-organismo como *L. monocytogenes* esseva basate super su hemolyse de sanguine ovin, su fermentation de sucro, e su pathogenicitate in muses. Le restablimento del patiente esseva complete post le uso de penicillina, chloramphenicol, e streptomycina. Es signalate le possibilitate—a causa de similaritates morphologic—de misprender *L. monocytogenes* pro diphtheroides contaminante con le resultante escappamento de illo al recognition como causa de morbo in humanos.

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EXTREME CARDIAC ENLARGEMENT *

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A PATIENT with rheumatic heart disease and acromegaly presented at postmortem examination an extremely large heart weighing 1,340 gm. The size of the organ was so striking as to remind an observer of hearts removed from steers in the abattoir. The case appears of sufficient interest to report in detail together with a review of the literature concerned particularly with massive car-

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diac hypertrophy. As Evans and White [1] have stated such case reports may assist by supplying information as to etiologic factors concerned with massive cardiac enlargement, in leading to a better understanding of the pathogenesis of cardiac failure in advanced heart disease.

Case Report

A 37 year old white male was admitted to the Oakland Veterans Administration Hospital on February 13, 1956, complaining of severe shortness of breath of three weeks' duration. He related that in 1944, while in the military service, he developed exertional shortness of breath, was hospitalized and told that he had a "valve leakage." He subsequently received a medical discharge for rheumatic heart disease. Three years later, in 1947, because of progressively increasing exertional dyspnea, he was prescribed digitalis for the first time, and his diet was restricted in salt. He was also forced to accept a more sedentary type of employment, in the form of office work. Over the next eight years he required three or four hospitalizations for treatment of acute cardiac failure, with progressive reduction in his exercise tolerance, so that walking up one flight of steps or walking too fast would cause him to stop to catch his breath. In 1955, approximately one year before admission to this hospital, he moved to the San Francisco Bay Area and accepted employment as a salesman for a local meat company. The job was quite fatiguing in that it required considerable traveling about in this area. Three weeks before entering the hospital he noted more marked exertional dyspnea, with frequent bouts of paroxysmal nocturnal dyspnea and orthopnea. He had been taking one digitalis tablet daily, but in the previous three months he had increased the dosage to two tablets daily. He denied cough, hemoptysis, chest pain or ankle edema. Past history was negative for rheumatic fever, hypertension or syphilis.

Another interesting point in the patient's medical history was the fact that for the previous 10 years he had noted distinct changes in the physical characteristics of his hands and face. There had been a gradual increase in both head and hand size, reflected in the need for larger sized hats and gloves. At the onset he had also suffered from frequent severe frontal headaches, but this symptom had subsided completely five years previously. He had also noted excessive sweating, heat intolerance, and a husky quality to his voice. He had not experienced any change in his libido, and denied symptoms of polyuria or polydipsia. Except for a hemorrhoidectomy in 1954, past history was otherwise not significant.

Physical Examination: The patient was a short, stocky man who looked older than his stated age, and was mildly dyspneic and orthopneic. He presented typical acromegalic features, with large head, prominent lower jaw with prognathism, large lips, nose, ears, hands and feet, and increased size of the chest with moderate dorsal kyphosis. There was a distinctly deep and husky quality to his voice. The blood pressure was 200/40 mm. of Hg; pulse rate, 68 per minute; respiratory rate, 24 per minute. Temperature was 96° F. The apical impulse was palpable in the sixth intercostal space at the midaxillary line, and the rhythm appeared to be totally irregular. He presented an aortic systolic thrill, a moderately loud aortic systolic murmur, and a diastolic murmur which could best be heard along the left sternal border. The chest was large and emphysematous, and moist râles were heard over both lung bases. The liver edge was palpable 4 cm. below the right costal margin and was slightly tender. Pressure over this organ caused the neck veins to become distended. Minimal pitting edema about the ankles was also noted.

Laboratory Studies: White blood count was 8,600; hemoglobin, 13.6 gm. (87%). Urinalysis showed a specific gravity of 1.022; albumin, 500 mg.%; sugar, negative; the sediment showed a few hyaline, granular and epithelial casts, and a few white

cells. Serologic test for syphilis was negative. Protein-bound iodine in the blood was 5.02 μg.%; circulating eosinophils, 33 per cubic millimeter; fasting blood sugar, 104 mg.%. A glucose tolerance test showed a fasting blood sugar of 98 mg.%; one-half hour, 162 mg.%; one hour, 162 mg.%; two hours, 115 mg.%; three hours, 85 mg.%. Simultaneous urine specimens obtained during this test were all negative for sugar. A 24-hour urine specimen representing a total volume of 2,600 c.c. showed 19.2 mg./24 hours as 17-ketosteroids, (normal for males, 4–43 mg.), and 9.1 mg./24 hours as total hydroxycorticoids as compound F (normal for males, 3.6 to 11.6 mg.).

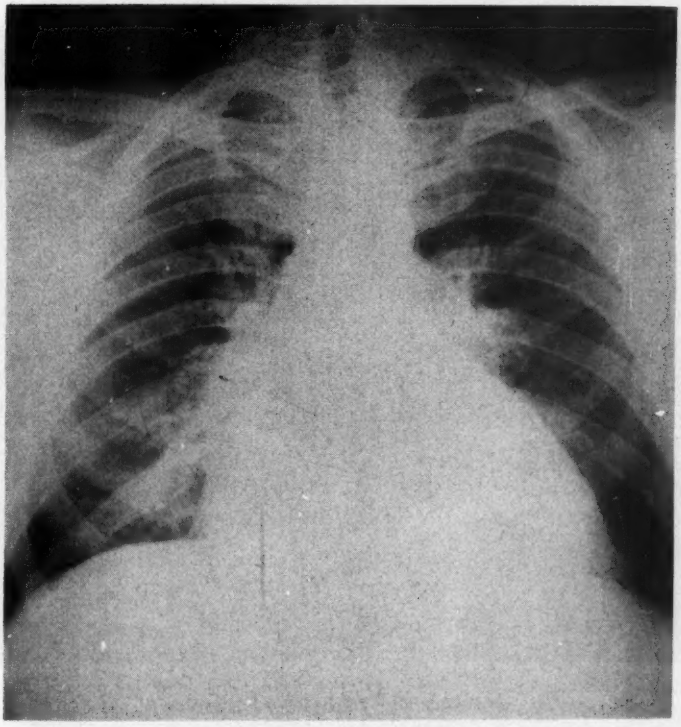

FIG. 1. Marked cardiac enlargement and pulmonary congestion.

Fluoroscopy and roentgenograms of the chest revealed marked cardiac enlargement (figure 1). Both ventricles were hypertrophied, and the left atrium was slightly prominent. The lung fields showed moderate congestive changes. Roentgenograms of the skull showed thinning and flattening of the posterior clinoids and deepening of the fossa of the sella turcica, suggesting enlargement as seen with pituitary tumor (figure 2). The sinuses were not enlarged, and there was no coarsening of the trabeculations of the skull or significant increased vascular markings in the cranium.

The electrocardiogram showed a basic pattern of left bundle branch block, with numerous multifocal ventricular ectopic beats.

Course: The patient was treated for cardiac decompensation with sodium restriction and bed-rest. Because the possibility of digitalis toxicity was suggested by the electrocardiographic findings and history of increased dosage over the last three months, digitalis was withheld, and he was treated with potassium chloride orally, 1 gm. three times a day for several days. Clinical improvement followed, with loss of dyspnea, pedal edema and lung râles. However, the numerous ventricular ectopic beats persisted, and remained unchanged following a trial of quinidine sulfate orally to a dosage of 0.6 gm. four times a day. Eventually he was redigitalized and discharged much improved, with diagnoses of rheumatic heart disease with aortic stenosis and insufficiency, and acromegaly.

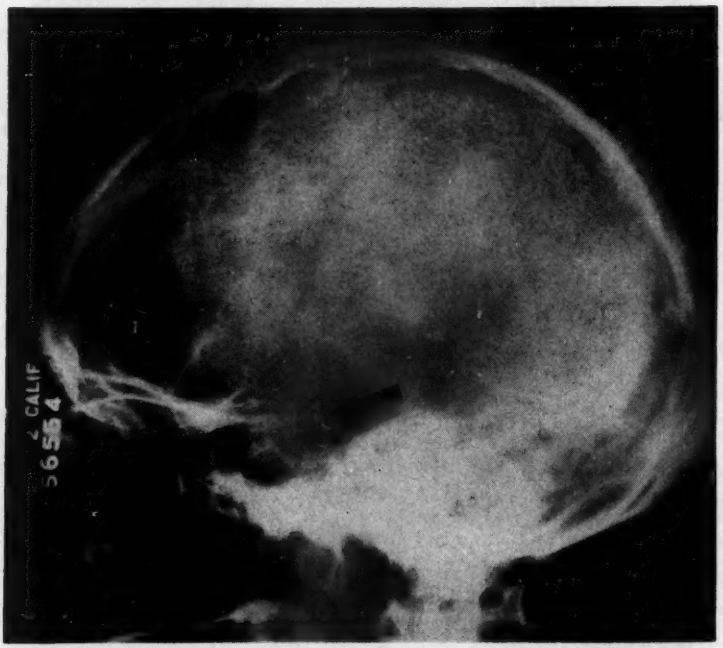

FIG. 2. Thinning and flattening of posterior clinoids and deepening of the fossa of the sella turcica suggestive of pituitary tumor.

Subsequent Course: About one month later the patient was re-admitted to the hospital complaining again of increasing shortness of breath, and showing signs of recurrent failure. He improved following the use of oxygen and mercurial injections, and was discharged two weeks later. He was re-admitted for the third and last time two weeks later, on May 12, 1956, complaining again of considerable dyspnea, recurrent anterior chest pains, and stomach gas pains for the last five days. On examination he appeared critically ill, with marked dyspnea and orthopnea. The blood pressure was 170/40 mm. Hg; pulse rate, 84, with numerous ectopic beats. The previously described aortic systolic and diastolic murmurs were again noted, as was an apical gallop rhythm. Advanced cardiac failure was manifested by râles in the lung bases, neck vein distention, liver enlargement and pedal edema. Chest roentgenogram revealed gross cardiac enlargement and congestive lung changes.

His congestive failure this time resisted therapy consisting of continuous oxygen, sodium restriction, mercurials and maintenance digitalis. During his rapid downhill course he drank considerable quantities of ice water, complained frequently of gas pains in the abdomen, and had frequent emesis and excessive perspiration. He eventually lapsed into coma and died on May 20, 1956, eight days after his final admission to the hospital.

Autopsy: The postmortem examination was performed by Dr. M. J. Smith, of the Department of Pathology, and disclosed the following pertinent findings. The

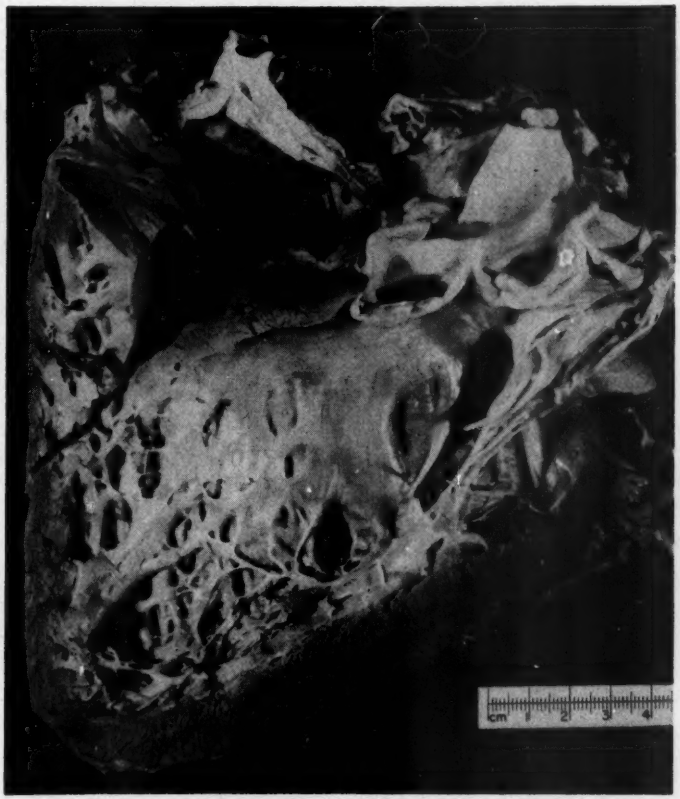

FIG. 3. Section through left ventricle, showing marked wall thickening and cavity dilatation, and thickening and shortening of the aortic valve.

body was that of a well developed and well nourished white male, measuring 68 inches in length and weighing about 175 pounds. The eyes were slightly protuberant and sclerae congested. Enlargement of the lower jaw, feet and chest was noted. When the usual Y-shaped incision over the anterior chest was made there were noted atrophy and fibrosis of the subcutaneous fat, which was dark brown in color. The musculature was well developed and beefy red in color. The peritoneal sac contained 800 c.c. of clear yellow fluid, and each pleural space contained about 50 c.c. of

similar fluid. The liver extended 4 cm. beneath the right costal margin in the midclavicular line.

The heart was markedly enlarged, weighing 1,340 gm. The epicardium and endocardium were not remarkable. The wall of the left ventricle measured 22 mm.; the right, 7 mm. The free edges of the aortic valve cusps were markedly thickened and shortened, and there were adhesions at the commissures, indicating an incompetency of the valve (figure 3). The other valves appeared structurally normal, although a dilatation of all the valves was indicated by the following measurements: aortic and pulmonic valve, 10 cm. in circumference; mitral, 13.5 cm.; tricuspid, 16 cm. The coronary arteries revealed a moderate, generalized atherosclerosis but without thrombosis. As the left ventricle was sectioned increased resistance to cutting was noted, although no gross scarring was seen, and the myocardium was

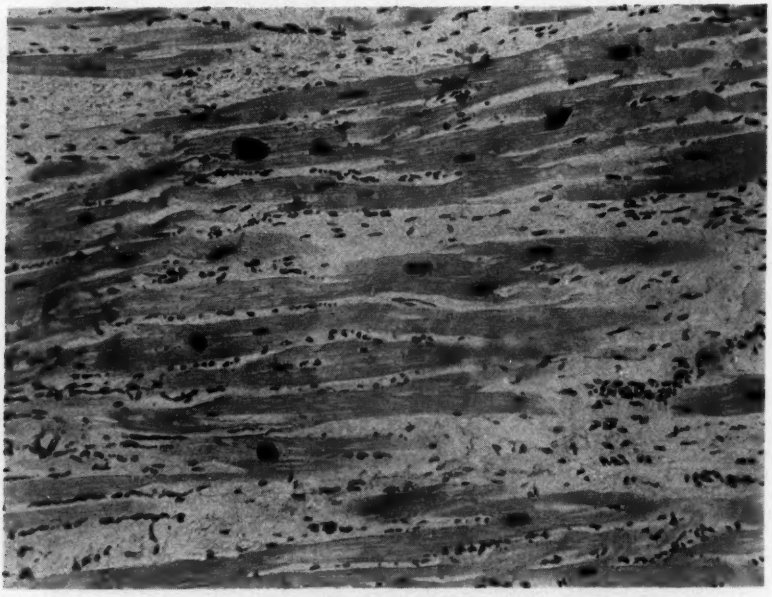

FIG. 4. Marked hypertrophy of the myocardial fibers and proliferation of the interstitial connective tissue (× 100).

beefy red in color. In the interventricular septum near the apex a small fresh scar was seen which measured 1.5 by 0.4 cm.

Both lungs showed marked congestion and exhibited a dark red parenchyma on cut surface. The left lung weighed 1,000 gm.; the right, 1,250 gm.

The liver weighed 2,900 gm. and showed marked congestion. The spleen weighed 660 gm. and was also congested. The left kidney weighed 310 gm.; the right, 260 gm. The pancreas weighed 140 gm., and cut with increased resistance. Both adrenal glands weighed 24 gm.; prostate gland, 32 gm.; thyroid, 25 gm.

The calvarium was markedly thickened, measuring 1 cm. The brain weighed 1,540 gm. There was a suggestion of a pressure cone on the under surface of the cerebellum. The sella turcica was markedly enlarged, measuring 33 mm. in width, 24 mm. in the anteroposterior diameter, and 10 mm. in depth. The anterior lobe of

the pituitary was almost completely replaced by tumor tissue which partially surrounded the right internal carotid artery and extended into the roof of the sphenoid bone. On sectioning, the tumor was noted to be firm in consistency, opaque white in color, and homogeneous without necrosis, hemorrhage or cyst formation.

Significant Microscopic Findings: Sections through the left ventricle revealed a marked hypertrophy of the myocardial fibers and proliferation of the interstitial connective tissue (figure 4). Several small scars were noted in the deeper myocardium, and attached to the endocardium were small antemortem thrombi undergoing organization. The right ventricle also revealed hypertrophy of the myocardial fibers. A section through the scar noted in the interventricular septum revealed this actually to represent multiple small scars which were infiltrated by a moderate

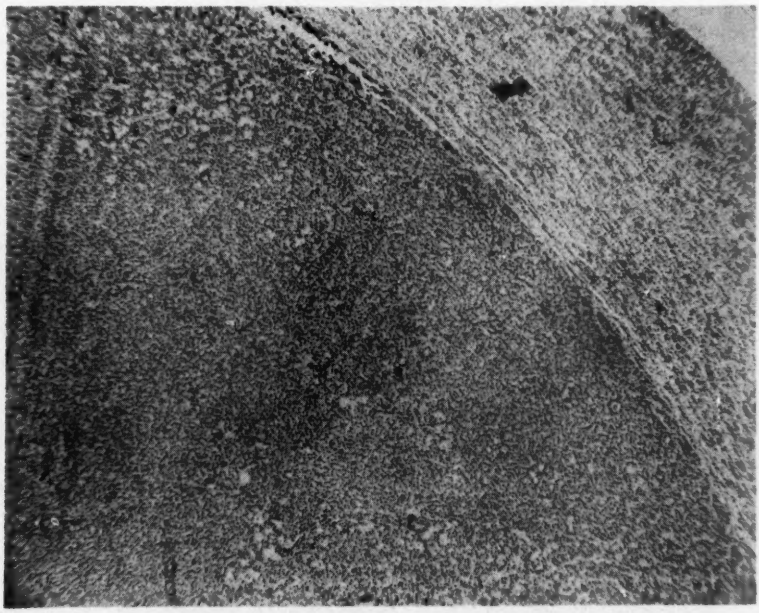

FIG. 5. Pituitary tumor well circumscribed but not encapsulated compressing an outer rim of normal gland (×25).

number of chronic inflammatory cells and richly supplied by capillaries. The free edges of the aortic valve cusps revealed moderate thickening and clubbing. There were scattered deep staining areas which were relatively acellular in the valve leaflet toward the peripheral portions, but the central portion took on a slight basophilic stain and was more cellular. There was no increase in vascularity within the valve, but slight increase in vascularity was present at the insertion of the valve. Here there were small capillaries surrounded by a few mononuclear cells, including a few cardiac histiocytes. There was some irregular scarring of the adjacent aorta but no cellular reaction. The endocardium was actually acellular, and in some areas there were degeneration and early calcification. The changes about the aortic valve were compatible with a healed rheumatic endocarditis.

The lungs showed marked congestion of the vascular bed. Numerous macro-

phages were scattered throughout the alveoli, many of which were filled with a finely divided and coarsely divided pigment, and there were some small intra-alveolar hemorrhages. In one of the sections there was a moderate sized artery filled with an antemortem thrombus composed of fibrin and red blood cells, fitting loosely into the lumen and not attached to the wall, regarded as an embolus, with considerable hemorrhage in the surrounding parenchyma. However, small hemorrhages were also seen in the other lung sections.

The liver and spleen showed characteristic congestive changes. The pancreas showed increase in fibrous connective tissue in the interlobular fat, and a few of the lobules were surrounded by bands of fibrous connective tissue which accounted for the increased resistance to cutting. The adrenals appeared to be normal in size, but there was a marked depletion of the cortical lipid plus congestive changes. The thyroid showed the follicles to be well filled with colloid.

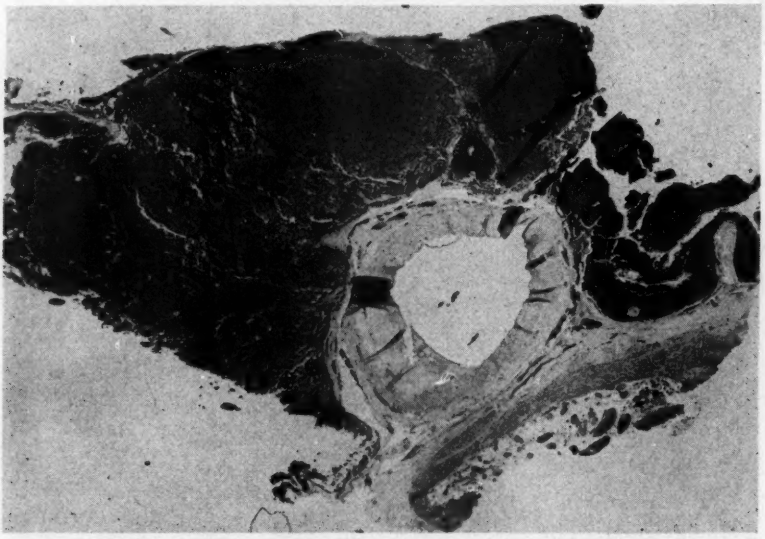

FIG. 6. Internal carotid artery partially surrounded by pituitary tumor (× 10).

Sections through the pituitary revealed a large tumor which had nearly replaced the entire anterior lobe, so that the remaining cells of the anterior lobe were somewhat compressed. The tumor was well circumscribed but not encapsulated (figure 5), and was composed of fairly large cells with ovoid and rounded vesicular nuclei. These cells showed a moderate amount of rather bright eosinophilic, granular cytoplasm. There was some pleomorphism present, and an occasional large nucleus. Cells formed solid sheaths, although a trabecular pattern was sometimes seen forming small irregular spaces but no true cyst formation. Cells with two and sometimes three nuclei were seen. One of the sections included the right internal carotid artery which was partially surrounded by tumor (figure 6).

Autopsy Diagnoses: (1) Healed rheumatic endomyocarditis; deformity of aortic valve (insufficiency); cardiac hypertrophy, right and left ventricle; myocardial scars, interventricular septum; pulmonary congestion and edema, bilateral; chronic passive congestion of liver, spleen and kidneys. (2) Eosinophilic adenoma of pituitary; acromegaly.

Discussion

The largest heart "on record" is supposed to have weighed five pounds (2,268 gm.). It does not stand as an authentic case report in the literature, but was first referred to by Sedgwick [2] in 1854. The case, however, is lacking in detailed information. The patient was described as a middle aged man who had suffered with heart disease for many years. The heart had been on display at the museum of the St. George's Hospital in London. Golden and Brams [3] relate that inquiry was made of the curator, who stated that the specimen had been lost and that no further information was available about either the heart or the patient. Sedgwick's case was that of a 26 year old female who had rheumatic heart disease and adhesive pericarditis and whose heart weighed 50¼ ounces (1,424 gm.). He also referred to other large hearts observed or recorded by contemporaries, the largest of these weighing 42 ounces (1,188 gm.). Other hearts might have been larger but details were too obscure, being described as either "enormous" or "as large as a bullock's."

In this country, antedating Sedgwick's report by four years, Smith [4] described an enlarged heart that weighed 58½ ounces (1,655 gm.). The patient was a 28 year old man who had been closely observed since the age of five, when he had had his first attack of rheumatic fever. The enlarged heart showed a left ventricular wall thickness of about 1 inch, and the cavity was estimated to be large enough to hold 8 or 10 fluid ounces. Both the aortic and the mitral valves were damaged, and a pericarditis was also present. The writer concluded that when hypertrophy begins at an early age the heart attains a size which an adult could scarcely carry had it begun at a later period.

An excellent review of the subject is supplied by Golden and Brams,[3] particularly as to cases documented before the turn of the century, a period during which knowledge and details were limited, with such diseases as syphilis not too well recognized and the blood pressure determination not a routine procedure. The writers, concerned with hearts exceeding 1,000 gm., present in concise table form 37 cases that were described previously, and to these are added nine cases of their own seen at Cook County Hospital from 1928 to 1937. Data on the 37 cases showed that all were males with only one exception. The most predominant lesions were adhesive pericarditis and deformity of the aortic valve, the largest hearts showing these lesions existing in combination. Of the writer's nine cases, the largest heart weighed 1,475 gm. and is described in detail as a case report. It belonged to a 33 year old Negro male laborer, and the etiology of the heart disease was recorded as idiopathic because of the absence of any apparent cause. Contrary to the earlier reports, there was only one instance of pericardial adhesions, but six cases did show aortic valve deformity as the predominant lesion.

Cabot,[5] in his monograph published in 1926, also pointed out the relationship of etiology to heart size. His material came from 1,906 necropsied cases of cardiovascular disease at the Massachusetts General Hospital from 1896 to 1919. He found that hypertension was the cause of hypertrophy and dilatation in 77% of cases, followed by rheumatic and syphilitic heart disease, in that order. Mitral valve involvement was more common as a single valve lesion than was any other single or combined valve lesion. An analysis of the 15 largest hearts in this series weighing more than 800 gm. showed chronic pericarditis to be an

important factor. It was found to be the sole factor in four of the five largest hearts, and a contributing factor in the fifth. The largest heart weighed 1,328 gm. and showed a chronic pericarditis with mediastinitis, rheumatic in origin. Aortic regurgitation was the next most common cause, followed by two cases without apparent anatomic cause. Mitral stenosis as a single lesion did not appear in this series of 15 largest hearts, the largest heart seen with mitral stenosis alone weighing 750 gm. However, multiple valve lesions of rheumatic origin produced six hearts that weighed more than 750 gm., which indicated that extreme enlargement did not occur in rheumatic heart disease unless the aortic valve was involved. Like mitral stenosis, hypertension, though the most common cause for hypertrophy, was not seen as a cause for extreme cardiac enlargement in this particular series.

However, in the report of Rosenow and Smith,[6] hypertension would appear to assume a more important role. In their series of 44 cases of hearts weighing 800 gm. or more, 20 had hypertension. The second most common group, consisting of 15 cases, had chronic rheumatic endocarditis with deformed heart valves. The third group, consisting of nine cases, was classified as miscellaneous. The largest heart weighed 1,170 gm. and showed calcified aortic stenosis, adhesive pericarditis and coronary sclerosis. In the hypertensive group of 20 cases, 19 were men, the largest heart weighed 1,100 gm., and the average weight was 831 gm. In the second group of 15 cases of chronic endocarditis, all men, the largest heart weighed 1,170 gm., and the average weight was 905 gm. In the miscellaneous group of nine cases, all men, the heart weights varied between 825 and 929 gm. Two cases were attributed to extreme obesity; two had syphilitic aortitis with aortic insufficiency; one had a congenital patent foramen ovale; one had an adenomatous goiter with hyperthyroidism, and three had severe coronary arteriosclerosis plus other contributing factors. In comparing their data with those of Golden and Brams,[3] the writers confirm the lesion of chronic aortic endocarditis as probably the most common cause for extreme cardiac enlargement in both series of cases, and the predominance of involvement in the male sex. The role of more than one or multiple factors in producing very large hearts is also stressed. For example, in 13 of the 20 cases of hypertension, obesity was present. In the 15 cases of chronic endocarditis, more than one valve involvement was the usual finding (six had aortic valve lesion only, the other nine had double valve lesions, aortic plus mitral, and, of these, six also had chronic adhesive pericarditis). In conclusion, it was noted that chronic aortic lesions produced the largest hearts; next was hypertension. Additional factors, such as double valve lesions, chronic adhesive pericarditis and obesity, contributed to the cardiac enlargement. One of the co-authors, Smith,[7] had previously devised a formula for estimation of normal heart weight for any patient of a known weight. This was obtained by multiplying the known body weight in grams by 0.43 for a man, and by 0.40 for a woman; or by multiplying the body weight in pounds by 1.96 for a man, and by 1.80 for a woman. However, the formula was said to be reasonably accurate only for patients who were near normal in weight, but did not hold for patients who were greatly overweight. Using this formula, Rosenow and Smith[6] compared actual pathologic weights to estimated heart weights according to the patient's weight.

In refuting the so-called Bernheim's syndrome, Evans and White[1] collected some interesting data on very large hearts. In 1910 Bernheim[8] had suggested

that right ventricular failure without significant hypertrophy could result from left ventricular hypertrophy of a marked degree. This could produce a bulging or intrusion of the septum into the right ventricle, resulting in a partial occlusion of that cavity, with consequent limitation in the amount of blood it could accept, and thus give rise to signs and symptoms of right heart failure, such as distended neck veins, congestion of the liver, dependent edema and cyanosis. The material for study was obtained from 2,000 consecutive autopsies performed in the five-year period from 1941 to 1946. There were 33 cases of marked cardiac enlargement with hearts weighing more than 750 gm. Of these, 28 weighed between 750 and 900 gm., and five exceeded 900 gm. The largest heart with the lesion of mitral stenosis weighed 1,350 gm. Although hypertension was the most common etiologic factor in these large hearts (14), the largest hearts resulted from rheumatic valvular lesions (eight). The majority of patients were men (29). Of the 33 cases, 22 fell into the category of left ventricular enlargement that conceivably could be responsible for producing Bernheim's syndrome. When clinical symptoms and postmortem findings were correlated not a single clear-cut case could be found to confirm the syndrome. From a theoretic standpoint it was felt that the thin-walled right ventricle should be able to dilate so that there would be no obstruction to blood flow; it was also felt that other reported cases of the syndrome could conceivably be the result of pulmonary disease, such as embolism or pulmonary hypertension.

Extreme cardiac dilatation with chamber enlargement from a volumetric standpoint is discussed by Bland, Balboni and White.[9] They reported a case of a 28 year old Italian male who died with long-standing mitral stenosis. Although his heart was enlarged from a weight standpoint (850 gm.), the more unusual feature was the extreme degree of dilatation, as shown by volume displacement of the filled heart, and the various chamber capacities. Volume displacement is obtained by filling the heart with fixing solution, ligating the main vessels, and then immersing the specimen and measuring the displaced water. The volume displacement in this case was 4,600 c.c., which is six to seven times that of a normal heart (700 to 800 c.c.) and stands as a record for future comparison. The capacity of the left atrium was very great—1,760 c.c.—exceeded by only three cases previously reported in the German literature. The right atrial dilatation and volume capacity measured 650 c.c. and were thought to be a record, with nothing reported larger than that. Right ventricular capacity was 320 c.c.; left, 70 c.c. According to Hochrein[10] the total capacity of the four chambers in the normal heart averages 561 c.c. The writers feel that such volumetric studies as performed in this unusual case should be done more often and thus serve as a helpful indication of the degree that cardiac dilatation plays in the production of cardiac enlargement.

The presently reported case, of a very large heart in a patient with both rheumatic aortic endocarditis and acromegaly, introduces a rare combination of etiologic factors. Acromegaly as a cause for cardiac enlargement is a generally accepted fact and frequently reported. Excellent reviews of the subject are supplied by Courville and Mason[11] and Hejtmancik, Bradfield and Herrmann.[12]

In 1895, just nine years after Marie[13] first described the features of acromegaly, Huchard[14] recorded his observations on three acromegalic patients and stated that cardiomegaly might be part of a generalized splanchnomegaly in this

disease, and could be secondary to generalized arteriosclerosis or caused by deformity of the spine and the thoracic cage. One year later, in 1896, Fournier [15] published a review of 25 cases of acromegaly and stressed the clinical picture of heart failure in some of these cases. Paviot and Beutter [16] in 1904 described the hypertrophy of the individual cardiac muscle fibers in an acromegalic patient who died of heart failure. Similar reports then appeared in both the French and German literature, summarized so well by Courville and Mason. In 1910, Humphrey and Dixon [17] reported a case of acromegaly in a 39 year old man who, in addition to the usual physical changes, presented evidence of heart disease. At necropsy the heart weighed two pounds 13 ounces (1,265 gm.), which probably is the largest acromegalic heart reported. In the absence of valvular disease or severe hypertension, the enlarged heart was attributed to the endocrine (pituitary) disorder. They proved on animal experimentation the presence of pressor substances in the urine and tissue in great excess, and postulated that these substances were in some way related to the hypertrophy of the heart as well as to the enlargement of the spleen and liver. Amsler [18] in 1912 similarly ascribed a hormonal origin to the cardiac enlargement. Bassoe [19] in 1922 found in acromegaly a general dilatation and sclerosis of blood vessels and adrenal hyperplasia, and postulated the presence of a pressor substance in the blood. These factors were thought to be of prime importance in the production of cardiac hypertrophy. The blood vessel changes had previously been stressed also by Sternberg [20] in 1899, particularly changes in the arteries which, as a rule, were dilated and thickened, with involvement of all three coats. In 1927 Cushing and Davidoff [21] described in one of their cases the presence of a marked increase in the supporting connective tissue of the myocardium, in addition to the hypertrophy of the cardiac muscle fibers; the larger blood vessels showed intimal thickening, but no changes were noted in the smaller vessels. The heart, in their case report, weighed 1,050 gm.

Courville and Mason [11] reported their observations on 24 acromegalic patients, of whom 18, or 75%, presented evidence of cardiac disease, six dying of heart failure. The largest heart of the six necropsied cases weighed 1,200 gm. (the others weighed 1,140, 850, 580, 500 and 400 gm.). They postulated that the enlargement of the heart was in part due to work hypertrophy. The increased work was caused by the abnormal growth of other organs and tissue. In part they felt that a pituitary hormonal effect on the myocardium might cause the hypertrophy. These authors could not confirm the presence of microscopic changes in the heart, such as increase in muscle fiber size and connective tissue, as being characteristic of the disease. Krauss,[22] however, felt that proliferation of interstitial tissue was an important change seen in this disease and accounted for the generalized splanchnomegaly; similarly, proliferation of fibrous tissue and epidermis was said to account for the thickening of the nose, ears, lips and eyelids.

A recent and, perhaps, the most comprehensive review on the subject is presented by Hejtmancik, Bradfield and Herrmann.[12] Their own study consisted of 21 acromegalic patients, including four necropsy protocols. Their particular interest in the disease was to evaluate more clearly the cardiovascular aspects, including electrocardiographic changes in those who presented evidence of heart disease for which no cause other than the acromegaly could be found. Of the 21 cases, 13 presented evidence of heart disease. The most common

abnormal electrocardiographic changes were impaired intraventricular conduction (six) and a left ventricular hypertrophy pattern (two). Six patients had hypertension, four had elevated basal metabolic rates, and five had diabetes mellitus. The four cases that came to necropsy showed cardiomegaly, the largest heart weighing 1,140 gm. Microscopically the myocardial fibers were hypertrophied, and in two of these cases there was conspicuous fibrous tissue proliferation. Pituitary or hormonal influence as a direct effect on the heart was felt to be the predominant factor in cardiac hypertrophy and interstitial fibrous tissue proliferation. A contributing factor was an increased work demand on the heart as a result of abnormal growth (by hormonal action) of other organs and tissues. The presence of thyrotoxicosis and impaired glucose metabolism in some cases might also be considered a contributing factor. It was not too clear what part hypertension played in the cardiopathy, but it could be stated that it was not too well tolerated. A similar concept had been advanced previously by Selye,[23] who also felt that, although the role of hypertension in acromegaly was obscure, the acromegalic heart did not tolerate it well, and it was in this association that the extremely large hearts and early cardiac decompensation was sometimes found. Although only six of his 21 cases had hypertension, it was conceivable that hypertension could have been a temporary or transient state and "burned out" at time of admission to the hospital, as was noted in one case with a 10-year follow-up.

Summary

1. A case is reported of an extremely large heart—weighing 1,340 gm.—in a patient with rheumatic aortic endocarditis and acromegaly.

2. A review of the literature concerned with extreme cardiomegaly in general, and specifically as related to acromegaly, is presented.

3. The overwhelming predilection to the male sex is stressed.

4. From an etiologic standpoint the most common causes for extreme cardiomegaly are aortic and mitral valvulitis as single or combined lesions, adhesive pericarditis, hypertension, and a miscellaneous group in which acromegaly is included. In many instances a combination of etiologic factors, such as occurred in the case reported, is likely to produce a very large heart.

Summario in Interlingua

Un extrememente allargate corde—de un peso de 1.340 g—esseva observate recentemente al examine post morte de un patiente con rheumatic morbo cardiac e acromegalia. Le caso es reportate in detalio. Le litteratura pertinente, specialmente in tanto que illo concerne massive allargamento cardiac, es summarisate.

Le patiente—un masculo de 37 annos de etate—esseva admittite al hospital in sever disfallimento congestive. Circa 12 annos previemente, in 1944, un examine del patiente habeva resultate in le diagnose de rheumatic morbo cardiac. Durante le intervallo, ille habeva essite hospitalisate e tractate plure vices pro recurrentias de disfallimento. In 1946 ille comenciava disveloppar typic aspectos e symptomas de acromegalia. Le examine del patiente a iste tempore monstrava le murmure diastolic de insufficientia aortic, marcate grados de allargamento cardiac, disfallimento congestive, e allargamento del sella turc in roentgenogrammas cranial. Ille non respondeva al therapia usate e moriva. Le necropsia revelava le marcate allarga-

mento cardiac, rheumatic insufficientia aortic, e un adenoma eosinophilic del corpore pituitari.

Ab le puncto de vista etiologic, le revista del litteratura revela que le principal causas de cardiomegalia extreme es morbo de valvula aortic e de valvula mitral (individualmente o in combination), pericarditis adhesive, hypertension, e un gruppo de factores miscellanee que include acromegalia.

Acromegalia como causa de allargamento cardiac es un definitemente establite facto clinic. Es postulate que le mechanismo causal del allargamento age per (1) un directe effecto hormonal (pituitari) super le corde, effectuante hypertrophia del fibras myocardial e proliferation del histos fibrose interstitial e (2) un effecto indirecte super le corde, representate per le demanda de un augmento del labor in consequentia del crescentia anormal de altere organos e histos sub le influentia del mesme effecto hormonal.

In multe casos de extreme allargamento cardiac, un combination de factores etiologic—ben illustrate per le patiente del presente reporto—es implicate in le genese del condition. Es etiam signalate le grande predominantia del sexo mascule.

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THE TOXICITY OF 2-HYDROXYSTILBAMIDINE: PROBABLE FATAL TOXIC REACTION DURING TREATMENT OF BLASTOMYCOSIS *

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Following the original report of Schoenbach et al.[1] of the successful therapy of a case of systemic North American blastomycosis treated with the aromatic diamidine, stilbamidine, numerous publications have attested to the efficacy of this drug in the treatment of blastomycosis and other mycotic infections.[2-10] Due, however, to the high incidence of trigeminal neuropathy in patients receiving stilbamidine, it is frequently necessary to discontinue the drug before a full therapeutic effect is attained.[2, 5, 11-13] More recently, other reports of the successful use of a stilbamidine derivative, 2-hydroxystilbamidine, in the therapy of these diseases have appeared.[5, 10, 14-17] No serious toxic reaction to the latter drug has ever been reported.[2, 14-16, 18] It is the purpose of this paper, however, to describe a fatal case of systemic blastomycosis in a seven year old Negro girl treated with 2-hydroxystilbamidine, whose death is believed to have occurred as a direct result of the toxic action of the drug given in relatively high dosages.

Case Report

A seven year old Negro girl was admitted to The Children's Hospital on May 29, 1955, with a three-day history of fever, productive cough, vomiting and progressively increasing lethargy. Past history revealed that she had been in good health until three months prior to admission, when she developed "pneumonia," which was treated by her private physician with penicillin, streptomycin and oxytetracycline. She apparently recovered from this illness but continued to have a nonproductive cough, accompanied by a relatively poor appetite and night sweats until admission. One month prior to admission a "lump" developed on her left hand. This lesion was incised and purulent material expressed, but it had never completely healed and at intervals discharged pus. Nine days prior to admission the patient contracted measles, which subsided uneventfully but was followed three days prior to admission

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by the development of fever. Her cough became productive of moderate quantities of greenish sputum and was associated with vomiting and abdominal pain. Over the three-day period immediately preceding admission she became progressively more lethargic.

Previous childhood illnesses included chickenpox and whooping cough, from which she recovered without complication. Her father, mother and five siblings were living and well. There was no familial disease history.

Physical examination on admission to the hospital revealed a well developed, well nourished Negro girl who appeared acutely ill and in moderate respiratory distress. Rectal temperature was 102° F.; pulse rate, 140; respiratory rate, 36 per minute. Admission weight was 42 pounds. Examination of the lungs revealed dullness to percussion, diminished breath sounds and a few moist râles in the lower two thirds of the right posterior lung field. There was a small healing ulceration present on the dorsum of the left hand. The remainder of the physical examination was noncontributory.

Initial laboratory investigation revealed a blood hemoglobin of 9.4 gm. per 100 ml.; hematocrit, 32%; white blood count, 28,600 per cubic millimeter, with a differential count which showed a shift to the left. Admission urinalysis was normal. X-ray of the chest at the time of admission demonstrated a homogeneous density covering the lower one-half of the right lung field, causing a slight displacement of the heart to the left. Numerous scattered areas of miliary calcification were seen in the pulmonary parenchyma bilaterally.

The original diagnostic impression was right lower lobe pneumonia with probable complicating empyema. The patient was treated with penicillin and chlortetracycline. The fever slowly subsided, and the temperature became normal 12 days after admission. Thoracentesis performed shortly after admission did not reveal any pleural fluid. A tuberculin skin test was negative and remained so during repeated testing throughout the hospital course. With subsidence of her fever the patient appeared markedly improved. However, since there was no improvement in either physical or roentgenographic findings, further investigation into the etiology of the pulmonary lesions was undertaken. Histoplasmin skin test was originally negative; repeated two weeks later, it was moderately positive. Three gastric washings were negative for pathogenic organisms. Scalene lymph node biopsy revealed only chronic inflammatory tissue. Bronchography demonstrated a filling defect of the right middle and lower lobe bronchi. The left lung appeared to have a normal bronchial tree. Bronchoscopy performed on June 20, 1955, did not show any distortion of the bronchial tree of the right lung.

On June 27, 1955, following a blood transfusion, a right thoracotomy was performed. At operation a generalized infiltration was present throughout the lower two thirds of the right lung. The right middle and lower lobes were grossly adherent to the chest wall, and the right hilar lymph nodes were moderately enlarged. Due to the extensive nature of the disease, bilobectomy was not attempted, but a wedge biopsy of the involved tissue and an azygous node were removed for histologic study. The patient tolerated the operation well and had an uneventful postoperative course.

Microscopic examination of the tissue removed at operation revealed numerous caseous granulomata containing organisms morphologically resembling blastomycetes. Culture of a portion of this tissue on Sabouraud's dextrose agar and Littman's oxgall agar grew in pure culture organisms positively identified as *Blastomyces dermatitidis*. Complement fixation tests for fungi revealed negative reactions for histoplasmosis and coccidioidomycosis but a positive reaction for blastomycosis in a dilution of 1:32.

A diagnosis of blastomycosis having been substantiated, therapy with 2-hydroxystilbamidine was instituted on July 16, 1955. An intravenous dose of 225 mg. of

this drug dissolved in 200 ml. of 5% glucose in normal saline was administered daily. The solution was always freshly prepared and given within half an hour of preparation. The time needed for each intravenous infusion varied somewhat, averaging two to three hours, but on no occasion did it take longer than eight hours. Although no special precautions were taken to shield the solution from sunlight, the patient was always kept in a shaded ward and was never directly exposed to the rays of the sun.

After several days of therapy the child complained of headache and nausea during and immediately following the daily dose of the drug. These complaints were frequently accompanied by a fever of 101° to 103° F., which subsided spontaneously after several hours. As these symptoms were considered to be side-reactions to the drug, the rate of administration of the drug was decreased; after the tenth day of therapy, all side-reactions ceased. Medication was continued without interruption (except for a five-day period when it was temporarily unavailable) from July 16 to August 21, 1955. Due to the lack of roentgenographic evidence of improvement of the pulmonary lesions, 450 mg. of the drug (in two doses of 225 mg. each at 12-hour intervals) were administered on two days (August 16 and 18). Total dose of 2-hydroxystilbamidine given over a 36-day period was 7.65 gm.

Following the decrease in the rate of injection of the drug, febrile reactions were no longer encountered. Throughout the course of therapy, however, the patient became intermittently anoretic and occasionally vomited. On August 19 it was observed that she was somewhat listless. She refused her diet and subsisted mainly on liquids, much of which she vomited.

On August 22, without warning, the patient suddenly experienced a grand mal convulsion. Blood carbon dioxide combining power at this time was 21 vol.%. All medication was discontinued and intravenous fluid therapy for correction of the acidosis was instituted. Following control of the convulsive episode with intravenous barbiturates, the child awoke, became oriented, and accepted oral fluids. Convulsions recurred, however, and almost continuous barbiturate therapy was necessary for their control.

Laboratory data on August 24, 1955, revealed a blood hemoglobin of 11.8 gm. per 100 ml., hematocrit of 40 and white blood count of 11,300 per cubic millimeter, with a predominance of polymorphonuclear cells. The urine was acid and otherwise normal. Blood carbon dioxide combining power was 30 vol.%; serum sodium, 128.5 mEq./L.; serum potassium, 2.8 mEq./L.; and serum chloride, 89.6 mEq./L. Blood nonprotein nitrogen was 30 mg. per 100 ml.; serum phosphorus, 5.2 mg. per 100 ml.; serum calcium, 8.5 mg. per 100 ml. Intravenous therapy was continued. On August 24 a rectal temperature of 101° to 103° F. was recorded, and her liver became palpable 1 cm. below the right costal margin.

Urinalysis performed on August 25 revealed an acid reaction; specific gravity, 1.030; 200 mg. of albumin per 100 ml; 3 plus sugar; 2 plus acetone, and a few granular casts. Cisternal puncture revealed slightly bloody fluid containing 20,000 red blood cells and 52 white blood cells (86% polymorphonuclears, 14% lymphocytes), protein of 30 mg. per 100 ml., and sugar of 27 mg. per 100 ml. Liver function tests revealed a cephalin flocculation of 4 plus at 24 hours, thymol turbidity of 9 units, total bilirubin of 1.4 mg. per 100 ml. (0.9 mg. direct and 0.5 mg. indirect), and a total protein of 5.7 gm. per 100 ml., with 3.7 gm. albumin and 2.0 gm. globulin (A/G ratio, 1.9/1.0).

Terminally, convulsions became more frequent and more difficult to control, and the child died on August 26, 1955.

Autopsy Findings: Postmortem examination was performed three hours after death. The body was that of a fairly well nourished and well developed Negro female weighing 20.5 K. The skin appeared normal. There was no scleral icterus.

Examination of the throat revealed the larynx and trachea to be normal. The pericardial cavity contained a small amount of clear amber fluid. The heart weighed 95 gm., and no abnormalities of the heart or great vessels were seen. The right lung weighed 176 gm. (normal, 130 gm.); the left lung weighed 157 gm. (normal, 123 gm.).

The pleural surfaces of both lungs were studded with raised, firm, gray, well circumscribed nodules averaging 0.3 cm. in diameter. The right middle and lower lobe bronchi were surrounded by dense grayish red pulmonary tissue which on section revealed irregularly circumscribed gray, firm, airless areas measuring up to 3.0 cm. in diameter. Section of the right and left upper lobes demonstrated numerous small gray miliary lesions. The left lower lobe was normal.

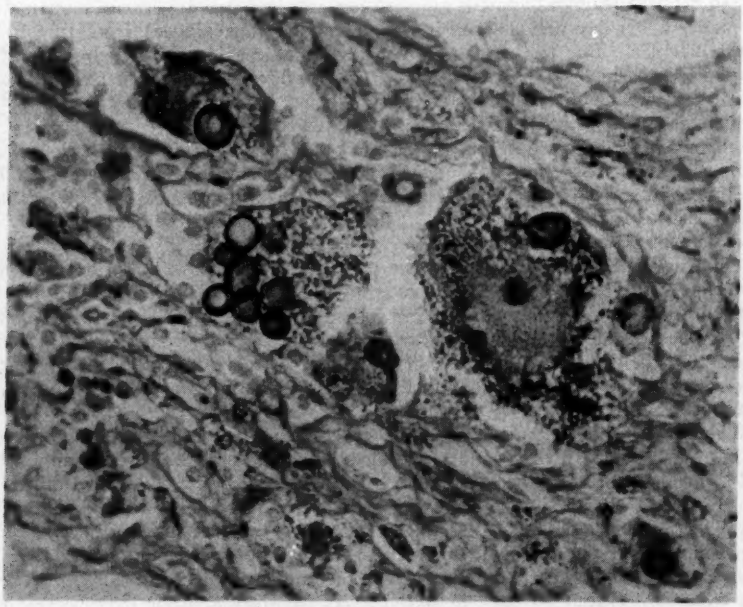

FIG. 1. Microscopic section of the lungs, showing giant cells containing numerous *Blastomyces dermatitidis* organisms. × 500. Gomori stain.

The tracheobronchial and retromediastinal lymph nodes were pinkish gray and averaged 2.0 cm. in diameter. These were hard, partially caseous and calcified on section.

The liver weighed 764 gm. (normal, 680 gm.). Its surface was light yellow and smooth. On section it appeared markedly yellow, and the portal pattern was indistinct.

The spleen weighed 59 gm. (normal, 66 gm.), and was dark purple in color. On section, the malpighian corpuscles were prominent.

The right kidney weighed 92 gm., the left kidney, 84 gm. (normal, 69 and 68 gm., respectively). On section, the kidneys were yellowish pink in color. There was good corticomedullary demarcation.

The stomach contained about 500 ml. of dark green fluid material but otherwise

appeared normal. The remainder of the gastrointestinal tract appeared unremarkable.

The brain weighed 1,348 gm. (normal, 1,263 gm.). The cerebral hemispheres were congested and slightly edematous. The gyral pattern and sulci were normal. Coronal section revealed no abnormalities.

The pancreas, adrenals, bladder, genital organs, abdominal lymph nodes and bone marrow were grossly normal.

Microscopic Examination: Heart: Widely dispersed throughout the myocardium of the ventricles were collections of amorphous basophilic granules located within the cytoplasm of some of the myocardial fibers. These granules were arranged in a linear pattern and were without any particular relationship to the nuclei.

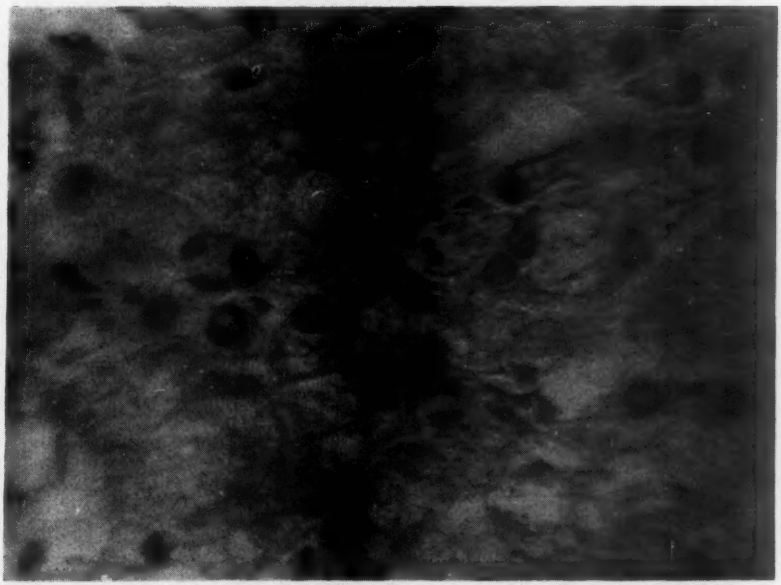

FIG. 2. Microscopic section of the liver, showing vacuolation and basophilic granulation of the individual hepatic cells. × 430.

Lungs: The pleura was irregularly thickened. The parenchyma was distorted by multiple granulomatous lesions containing giant cells of the Langhans type and double-walled structures several times the diameter of red blood cells. These latter structures appeared to be transparent with routine hematoxylin and eosin staining, and were reddish lilac in color with the Gridley stain. These organisms were identified as *B. dermatitidis* (figure 1). There were many areas of dense fibrosis, calcification and acute inflammatory exudate scattered throughout the entire right lung and the left upper lobe. In other sections there were large areas of bronchopneumonia and emphysema. Review of the microscopic sections of pulmonary tissue was performed by Dr. L. E. Zimmerman, of the Armed Forces Institute of Pathology. In addition to blastomyces organisms located throughout the pulmonary parenchyma, he observed some small areas in the lungs and hilar lymph nodes which contained focal, discrete, encapsulated fibrocaseous granulomas which contained organisms resembling *Histoplasma capsulatum.*

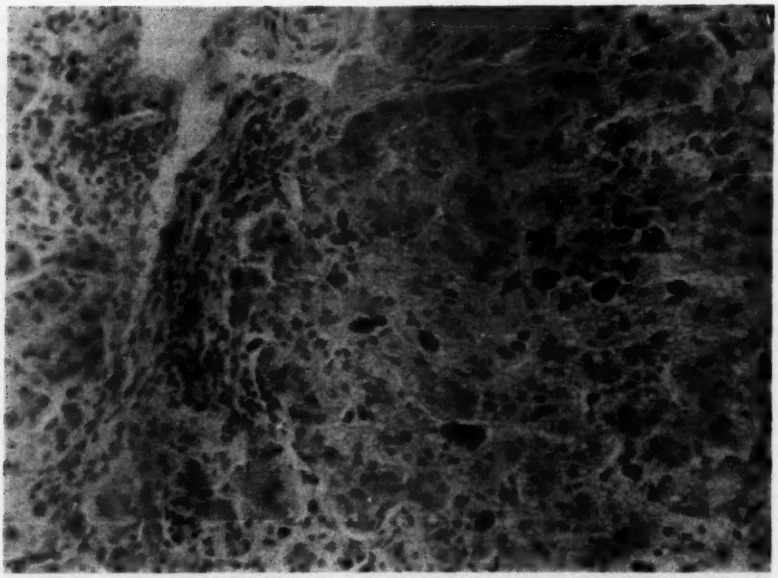

FIG. 3. Microscopic section of the liver, showing the Kupffer cells engorged with deeply staining basophilic material. × 115.

FIG. 4. Microscopic section of the adrenal gland, showing extensive basophilism of the cells of the zona glomerulosa. × 115.

Liver: (figure 2): There was generalized vacuolation of the liver cells, only a few escaping involvement. This vacuolation was not confined to any portion of the lobules, the central, midzonal and peripheral areas being equally involved. The vacuoles were small and finely dispersed in the cytoplasm of the cells; the average number in each cell was eight. The majority of the vacuoles were equal in diameter to the hepatic nucleus, the hepatic cells themselves being two to three times normal size. Within most of the cells were coarse basophilic granules, somewhat larger than those found in the myocardial fibers. A significant feature was the prominence of the Kupffer cells, which were engorged with deeply staining basophilic material (figure 3).

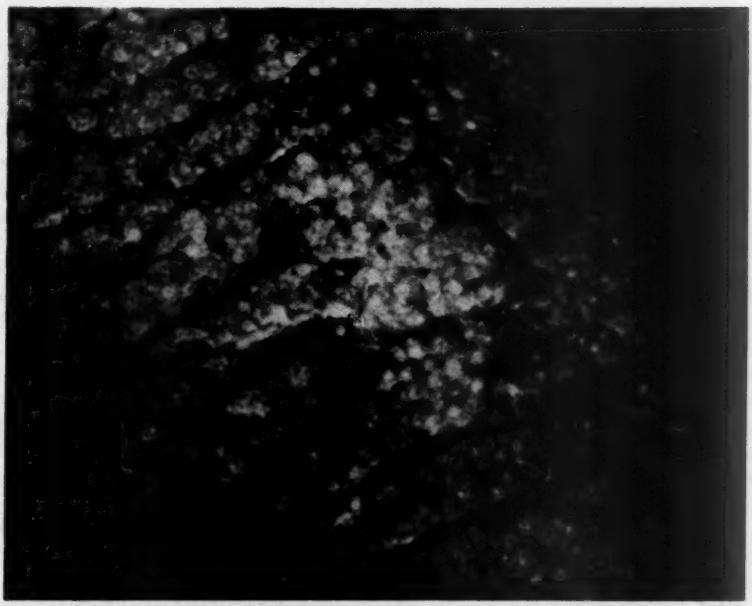

FIG. 5. Microscopic section of the cortex of the adrenal gland, photographed through a fluorescent microscope and showing intense fluorescence of the cortical cells. × 240.

Spleen: The sinusoids were moderately congested. The lymphoid follicles were not remarkable except for an occasional reticulum cell showing fine basophilic stippling of the cytoplasm.

Adrenals (figure 4): Massive basophilic granularity was present in all zones of the cortex but to a somewhat greater extent in the zona glomerulosa. The cells of the latter zone also showed early degenerative changes. There was a minimal degree of vacuolation of the cells in all zones of the cortex. The medulla was unremarkable. Oil red O staining demonstrated the presence of fat in all zones but to a greater degree in the zona fasciculata.

Kidneys: The glomeruli were unremarkable. There was coarse vacuolation of the epithelial cells of the tubules, most evident in the proximal portion. In both proximal and distal tubule cells were scattered areas showing basophilic granules in the cytoplasm. The collecting tubules contained the greatest accumulation of fine basophilic granules.

Bone Marrow: There was scattered basophilic granularity in some of the reticuloendothelial cells.

Brain: An occasional ganglion cell in the cerebral cortex showed fine basophilic granularity of the cytoplasm.

The thymus, thyroid gland, pancreas, bladder, gastrointestinal tract, generative organs and spinal cord showed no remarkable changes.

Organs demonstrating the most marked pathology were the lungs, liver and adrenal glands and, to a lesser extent, kidneys, heart, spleen, cerebral cortex and bone marrow. The lungs were extremely involved with the lesions of blastomycosis but otherwise showed little evidence of specific cellular changes.

The liver demonstrated a severe degree of fatty infiltration and degeneration, as evidenced by widespread vacuolation. This process also involved the tubules of the epithelium of the kidney, but to a less marked degree. A striking feature was the presence of small, dense basophilic granules in the cytoplasm and the nuclei of hepatic cells, the tubular epithelium of the proximal convoluted tubules and the cortical cells of the adrenal gland. These granules were also seen in lesser amounts in the myocardium and occasionally in ganglion cells of the central cortex and reticulum cells of the spleen and bone marrow. Exposure to ultraviolet light caused strong fluorescence of the tissues (figure 5).

Discussion

2-hydroxystilbamidine di-isethionate exists as a yellow crystallized powder which is highly soluble in water or isotonic dextrose and saline solutions. Both powder and solution undergo slow decomposition by hydrolysis of the amidine groups when exposed to ultraviolet light. The decomposition products are insoluble and may cause the solution to become turbid. In addition, an estimated increase in toxicity of approximately 50% occurs following exposure to sunlight.[5] However, 2-hydroxystilbamidine in solution has been shown to be much more stable than solutions of stilbamidine, where a 600% increase in toxicity has been demonstrated after two days in solution. For this reason, it has been recommended that both stilbamidine and 2-hydroxystilbamidine in solution be protected from sunlight by thick brown paper and the patient not be allowed to expose himself to strong sunlight for at least one or two months following discontinuance of therapy.[5]

Both compounds are promptly absorbed and leave the circulation rapidly. They are then stored in large amounts in the parenchymatous organs, principally liver, kidneys and adrenal glands.[2, 19, 20] Initially, not more than 10% of the injected amount of drugs is excreted in the urine.[2, 19, 21] After eight days of therapy, however, when the tissues have presumably become completely saturated with either drug, urinary excretion rises sharply to 75 to 85% of the injected amount.[12] Once deposited in the cells, these drugs do not entirely leave the tissues for months or years, and may exert an effect long after cessation of therapy.[2, 16, 19]

In the adult, the recommended daily dose of 2-hydroxystilbamidine is 225 mg. of the powder freshly dissolved in 250 to 500 ml. of 5% dextrose in distilled water. The solution is administered by intravenous infusion immediately after preparation and given for an initial period of 30 days. After a short rest period, a repeat course may be given if necessary. If freshly prepared and protected from sunlight, large doses have been given with no evidence of serious toxicity.[16] Sutliff [5] has administered a daily dose of 450 mg. to adults with blastomycosis, one of his patients receiving 45.2 gm. of 2-hydroxystilbamidine over a 13 month

period with no apparent toxic manifestations. Snapper [16] has estimated a safe total dosage to be 0.3 to 0.4 gm. per kilogram of body weight. In children the recommended daily dose is 3 mg. per kilogram of body weight.

Minor reactions to 2-hydroxystilbamidine occur fairly frequently. Circulatory collapse may take place either during or immediately following too rapid intravenous infusion, or with solutions of high concentration. These reactions may be obviated by slowing the rate of administration or increasing the dilution of the drug in solution.[5, 16] Formication will also occasionally occur when the drug is injected too rapidly. Weakness, headache and myalgia have been reported in some cases after total amounts of 10 to 14 gm. have been administered. These complaints subside with shorter courses of therapy and longer rest periods.[5, 16] In the therapy of coccidioidomycosis with 2-hydroxystilbamidine, nausea and vomiting occur fairly regularly and appear to be directly attributable to the action of the drug. These symptoms become progressively more severe with increased total dosage, but will also subside with shorter courses of therapy and longer rest periods between courses.[16] Nausea and vomiting have been unusual in blastomycosis treated with 2-hydroxystilbamidine. All side-effects attributable to 2-hydroxystilbamidine are frequently more marked in patients with severe chronic infections or with constitutional complaints prior to therapy.

The toxic neuropathy commonly seen with stilbamidine therapy has never been encountered with 2-hydroxystilbamidine, even when high doses are given, and the neuropathy resulting from stilbamidine therapy may disappear when 2-hydroxystilbamidine is substituted.[2, 5, 14–16]

Kirk and Henry [12] observed fatal delayed poisoning in stilbamidine-treated patients with kala-azar. The symptomatology resembled that seen in sudden hepatic failure and occurred from one to three months after cessation of all therapy. These patients, who had apparently been cured of their disease, developed a sudden onset of nausea, vomiting and anorexia. Coma rapidly ensued and death commonly occurred in from one to four days. These fatalities were originally thought to have resulted from the cumulative action of the drug. It was later discovered, however, that old solutions of stilbamidine had been used in all fatal cases. Death was therefore attributed to the poisonous effect of the products of stilbamidine decomposition, chiefly the sulfate. The toxicity of this compound for mice has been found to be in conformity with that of irradiated solutions of stilbamidine.

Extensive laboratory study of patients receiving stilbamidine or 2-hydroxystilbamidine has failed to demonstrate any evidence of abnormality attributable to the drugs.[2, 5, 15, 16] Until recently, no impairment of liver or kidney function in otherwise uninvolved organs has ever been observed. Harrell et al.,[10] however, have reported "abnormal liver function tests" (without further description) in a patient with systemic blastomycosis treated with 2-hydroxystilbamidine. These abnormalities disappeared soon after discontinuance of the drug. Stilbamidine may precipitate uremia in patients with multiple myeloma.[11] This phenomenon, however, is apparently dependent upon the previous involvement of the kidneys with the lesions of multiple myeloma, since uremia has not occurred in the absence of involvement of the kidneys by the disease.

When experimental animals are given one-half the lethal dose of stilbamidine a resultant rise in blood urea nitrogen occurs.[11, 23, 24] With increase of the dose of stilbamidine to almost lethal amounts, a transient rise of 100% in blood sugar

appears. These hyperglycemic levels rapidly fall to normal, and actual hypoglycemia may occur terminally. With the larger doses of stilbamidine, there is prolonged impairment of renal function, with either transient or fatal uremia and death within 10 days. Small or therapeutic doses of stilbamidine in animals do not cause any change in the blood sugar level, although these same doses are capable of causing an elevation of blood urea nitrogen or blood nonprotein nitrogen. On the basis of these findings, renal damage is thought to occur before hepatic damage and independently thereof.

Postmortem examination of experimental animals given lethal doses of stilbamidine and 2-hydroxystilbamidine has revealed extensive fatty degeneration of the liver to be the most consistent finding.[11, 12, 22, 24] In no instance, however, is there hepatic necrosis of such degree as to produce acute yellow atrophy. Involvement of the kidney is also common. The most characteristic kidney lesions are swelling and degeneration of the epithelium of the convoluted tubules, as well as focal areas of medullary hemorrhage.[11, 12, 24-26] Kirk and Henry [12] have described an indefinite blue staining of the tubular epithelial cells which they believe is due to lysis of nuclear basophilic material.

Reports of examination of autopsy or biopsy material in humans who have previously received large doses of stilbamidine have failed to show conclusive evidence of renal or hepatic damage which can be attributed to the drug. Arai and Snapper [11] have reported five autopsies in patients who died of multiple myeloma and who had been treated with large doses of stilbamidine prior to death. In no case was there any evidence of liver or kidney damage which could not be explained by the primary disease. Kirk and Henry,[12] in reporting the toxicity of old solutions of stilbamidine used in the therapy of kala-azar, described the autopsy findings in six cases and the results of liver biopsy in an additional four patients. In the six autopsied cases, death was presumably due to the toxic effects of the drug. The kidneys were examined in only two of these cases. In both, the glomeruli appeared swollen and congested, and the tubular cells showed marked fatty degeneration. In seven instances liver necrosis was a prominent feature, but all of the patients had some degree of fatty degeneration of the liver. There were no definite pathologic findings in the myocardium or adrenal glands. The specificity of these autopsy and biopsy findings is in doubt, since the role of the primary disease in producing them was not determined.

In multiple myeloma patients treated with stilbamidine, Snapper and his coworkers [27, 28] noted the presence of large basophilic granules in the cytoplasm of myeloma cells obtained by bone marrow biopsy. These granules fluoresce strongly when examined under the fluorescent microscope, and have been shown to consist of stilbamidine linked with ribose nucleic acid present in the cell cytoplasm.[18] With 2-hydrostilbamidine injection, these fluorescent granules are also present in the cell nucleus, demonstrating the ability of this drug to penetrate the nucleus with the formation of a 2-hydroxystilbamidine-desoxyribosenucleic acid complex.[29]

Fluorescent microscopy has also shown that soon after injection of 2-hydroxystilbamidine into experimental animals, the nuclei of the cells of liver, kidney and adrenal glands (as well as other organs to a less marked degree) are strongly fluorescent.[19, 29, 30] This phenomenon has also been observed in human tissue.[30] In cancer mice, strong fluorescence of the nuclei of the cere-

bral ganglion cells has been noted. Stilbamidine has much less affinity for the cell nucleus than 2-hydroxystilbamidine, therapy with the former drug producing only faint nuclear fluorescence.

This affinity of 2-hydroxystilbamidine for cell nuclei is so great and the readiness with which it precipitates desoxyribosenucleic acid in vitro so marked that Snapper has commented that it is actually very surprising that such large amounts of the drug can be found in cell nuclei without any apparent disturbance in cellular function.[15]

Our patient received a total dose of medication within the range recommended by Snapper. However, the daily dose was approximately four times that recommended by the manufacturer. In retrospect, the gastrointestinal symptoms should have been interpreted as evidence of toxicity due to cumulative action of the drug rather than to drug side-effects. Since the drug solution was always freshly prepared, administered promptly, and not exposed to direct sunlight at any time, it is not felt that decomposition during administration played a role in producing toxicity.

The presence of abnormal liver and kidney function, together with clinical evidence of acute hepatic failure, leads us to believe that a direct toxic action of the drug was responsible for the patient's death. Since blastomycotic lesions were confined to the lungs and hilar lymph nodes, were not extensive and showed evidence of healing, it would not appear that the disease itself was directly responsible for the fatal outcome.

It is to be emphasized that, although this is the first reported case of serious toxicity to 2-hydroxystilbamidine, studies of hepatic and renal function as recommended by the manufacturer should antedate any administration of this drug. Periodic reëvaluation of liver and kidney status should be performed at weekly intervals throughout the course of therapy. Should any laboratory or clinical evidence of toxicity appear, the drug should be discontinued immediately and reinstituted only after a suitable rest period in which abnormal laboratory studies have returned to normal.

Summary

A fatal case is reported of North American blastomycosis in a seven year old Negro female, whose death is attributed to toxicity resulting from treatment with 2-hydroxystilbamidine. The literature concerning the toxicity of stilbamidine and 2-hydroxystilbamidine is reviewed. Death in this patient is believed to have occurred as a result of acute hepatic failure. A plea is made for strict adherence to the recommendation that periodic studies of hepatic and renal function be performed during the administration of 2-hydroxystilbamidine.

Acknowledgment

The authors wish to express their grateful appreciation to Dr. Frank B. Johnson, Chief, Histochemistry Section, Armed Forces Institute of Pathology, who examined autopsy material by fluorescent microscopy, and to Mr. Edward Riggs, of The Children's Hospital, who prepared excellent histologic sections.

Summario in Interlingua

Es presentate le prime reporto de un caso de morte occurrente probabilemente como resultato del toxicitate de 2-hydroxystilbamidina. Un puera negre de septe

annos de etate esseva hospitalisate con symptomas respiratori. Le examine physic e roentgenographic indicava consolidation del duo tertios inferior del pulmon dextere. Le examine histologic e culturas de specimens bioptic obtenite per thoracotomia exploratori revelava indicios convincente de infection per *Blastomyces dermatitidis*.

Esseva initiate therapia intravenose con 2-hydroxystilbamidina. Illo esseva continuate durante un periodo de 36 dies, representante un dose total de 7,65 g. Iste total esseva intra le limites recommendate pro le peso corporee del patiente sed le rapiditate del administration excedeva le norma recommendate per circa quatro vices.

Initialmente, diurne reactiones de febrilitate occurreva durante le administration intravenose del droga, sed istos subsideva post 10 dies de tractamento. Un mense post le institution del tractamento le puera habeva episodios de vomito e deveniva anorectic. Quatro dies ante su morte illa habeva un accesso de grand mal. Illa deveniva febril e su hepate deveniva palpabile pro le prime vice. Le convulsiones continuava periodicamente usque al morte.

Le constatationes laboratorial durante le ultime dies ante morte indicava le presentia de acidosis metabolic. Albuminuria e anormalitate in tests hepatic de flocculation esseva notate.

Al necropsia le lesiones del blastomycosis se monstrava restringite al pulmones e al nodos hilar. Esseva notate in illos nulle signo de resanation. Le hepate esseva allargate e de color levemente jalne. Microscopicamente, signos esseva trovate de vacuolisation generalisate del cellulas hepatic. Multes de istos contineva grossier granulos basophilic. Similemente, grossier vacuolisation e infiltration de granulos basophilic esseva constatate in le cellulas epithelial del tubulos renal. Grossier granulos esseva locate in omne zonas del cortice adrenal e etiam—a grados minus pronunciate—in altere organos. Es exprimite le opinion que le morte occurreva como resultato de disfallimento hepatic.

Es presentate un revista del litteratura concernite con le toxicitate de stilbamidina e 2-hydroxystilbamidina. A causa del augmentation del toxicitate de iste medicationes quando illos es preservate in forma de solution, il es necessari solver los frescamente e administrar los promptemente. Durante iste manipulation le solution debe esser protegite contra le lumine del sol, le qual—per promover le decomposition del drogas—augmenta le toxicitate del preparato.

Post su administration, 2-hydroxystilbamidina es deponite rapidemente in le cellulas. Illo non quita le histos completemente mesmo post menses e annos, de maniera que su effecto continua longemente post le cessation del therapia. Microscopia fluorescente revela que 2-hydroxystilbamidina es deponite primarimente in le nucleos cellular de hepate, renes, e glandulas adrenal, e isto in tal quantitates que il es surprendente que evidentia de su obstruction del functiones cellular non es plus abundante.

Le dose total de 2-hydroxystilbamidina non deberea esser extra le limites de 0,3 e 0,4 g per kg de peso corporee. Omne signo de non-tolerantia—per exemplo marcate grados de anorexia, nausea, o vomito—es un indication pro le prompte discontinuation del therapia. Post un appropriate periodo de reposo, le therapia pote esser recomenciate. Ante e durante le curso del therapia, evalutationes periodic del functiones hepatic e renal debe esser effectuate, e omne discoperta de un anormalitate debe esser interpretate como indication pro le cessation immediate del therapia usque le tests de function ha retornate a valores normal.

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ACUTE DISSEMINATED PULMONARY HISTOPLASMOSIS TREATED WITH CORTISONE AND MRD–112 *

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Epidemics of acute pulmonary histoplasmosis have been recognized with increased frequency in recent years. In 1957 Lehan and Furcolow collected 38 epidemics involving over 400 individuals.[1] Although many of the patients were seriously ill for weeks, there were only five deaths, and three of these were in children. The low mortality (1.2%) suggests that most patients develop adequate immunity.[2] They also develop an allergy of the tuberculin type to histoplasmin within the first two to three weeks of the disease.

In the case to be reported the patient was exposed to bat manure in a cave and apparently received a massive infection, since the early x-rays showed myriads of minute areas of infiltration scattered throughout both lungs. Simultaneously with the development of allergy to the fungus, the local lesions in the lungs increased in size and became almost confluent, thus threatening the life of the patient by a mechanical reduction in the available respiratory space. Cortisone was used to stop the allergic reaction about the infected areas, and beta-di-ethyl-aminoethyl-fencholate (MRD-112) was administered to prevent cortisone's inducing a generalized dissemination of the infection.[3, 4, 5]

Case Report

A 32 year old white male patient from Florida was admitted to Duke Hospital on July 31, 1955, complaining of shortness of breath, pleuritic pain and cough. The patient had been in his usual state of good health until July 13, 1955, when he awoke febrile and short of breath. A review of his family history and past history was noncontributory. Three weeks before his first symptom he had breathed in dust laden with bat manure while exploring a cave, and three days before the onset he had handled and buried a pet parakeet.

The patient had been treated with a variety of antibiotics between July 13 and July 31, without improvement. There was a progressive increase in dyspnea, which

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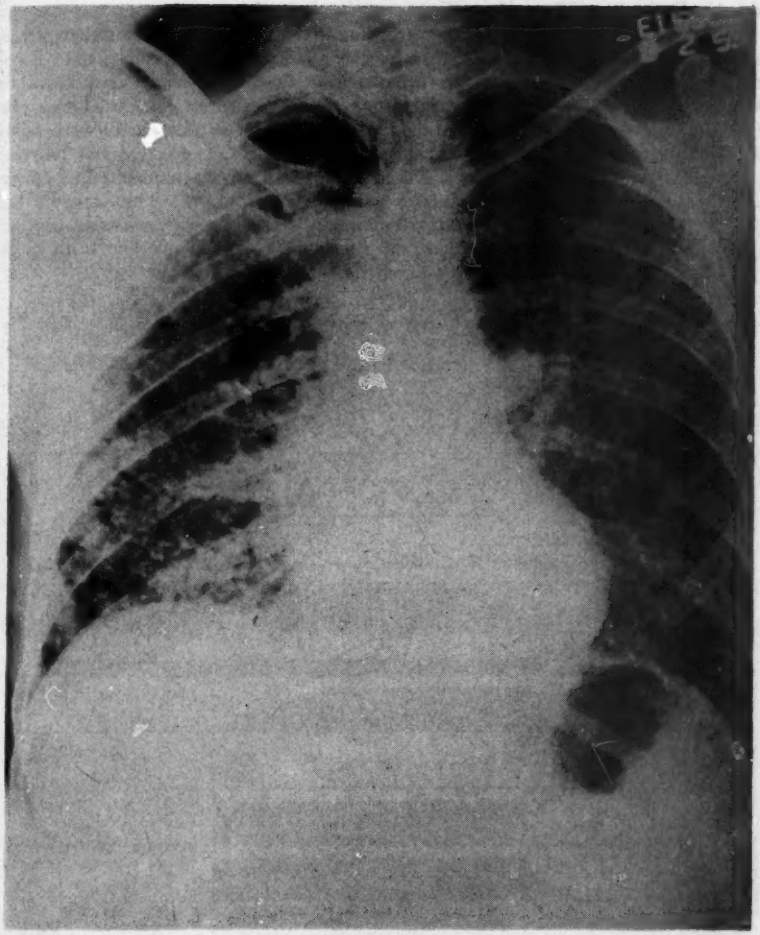

FIG. 1. X-ray of patient shortly after admission on September 2, 1955, when he was dyspneic and cyanotic.

was now accompanied by a nonproductive cough, pleural pain and night sweats. There were a severe anorexia and a weight loss of 30 pounds. A rather striking increase in symptoms occurred about the time the first positive skin test to histoplasmin was obtained, one week before admission.

Physical examination on admission revealed a cachectic, cyanotic young male in marked respiratory distress, breathing shallowly at the rate of 40/min. Blood pressure was 130/90 mm. of Hg; pulse rate, 80/min. His skin was dry and cyanotic. The nails of all extremities were cyanotic. The inguinal lymph nodes were easily palpable bilaterally, and were discrete and nontender. The patient's ears, eyes, nose and throat were not remarkable. His lips were cyanotic and his oral mucosa was dry. The neck was supple and easily flexed. His chest moved rapidly and shallowly,

without splinting of either side. There was a slight degree of tenderness on deep palpation over an area lateral to the precordium. There were no changes to percussion. Auscultation revealed moist biphasic râles and bronchial breath sounds spread widely over both lung fields but accentuated over the bases posteriorly. An intermittent pleural friction rub was heard by some observers over the left lower chest anterolaterally. Examination of the abdomen revealed generalized tenderness which could be broken through by persistent deep palpation. The liver edge was felt three fingerbreadths below the right subcostal margin. The spleen was enlarged to percussion. Rectal and genital examination was noncontributory. The patient's back and extremities were normal except for the already noted cyanotic nails and dry skin. Neurologic examination revealed a mentally alert and anxious patient with hyperactive but symmetrically equal deep tendon reflexes.

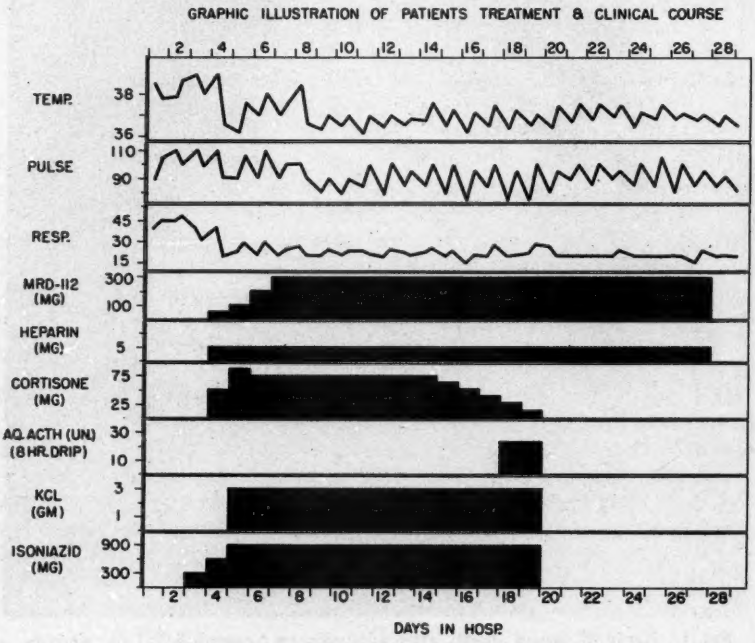

CHART 1.

Accessory Clinical Findings: Hemoglobin, 16.9 gm.; white blood cells, 11,500; differential: 81% polymorphonuclears; 2% stabs; 4% lymphocytes; 13% monocytes. Urinalysis revealed a transient trace of proteinuria. Stool examination was negative for ova and parasites but showed a trace of blood. Serologic tests for syphilis were negative. Histoplasmin skin test was 3 plus in 24 hours; OT (1:100), blastomycin and coccidioidin skin tests were negative in 48 hours. Complement fixation test for psittacosis was less than 1:1.

Wright's stain of sputum smears showed large monocytic cells with degenerating cytoplasmic inclusion bodies compatible with *Histoplasma capsulatum.* Smears of sputum for acid-fast organisms were negative. Admission chest film (figure 1) showed the lungs to be studded with small nodules bilaterally.

A presumptive diagnosis of histoplasmosis was made. The sputum was cultured for *H. capsulatum* on antibiotic-containing media, and blood serum was sent to both the Communicable Disease Center at Chamblee, Georgia, and the Walter Reed Hospital in Washington. The fungus failed to grow on our media. Subsequent reports from the Communicable Disease Center showed a complement-fixing titer for histoplasmosis of 1:8, and those from Walter Reed Hospital a titer of 1:128. Bat manure obtained from the cave in which the patient was exposed was sent to Dr. Norman F. Conant, of the Duke Hospital, who injected mice with samples of the

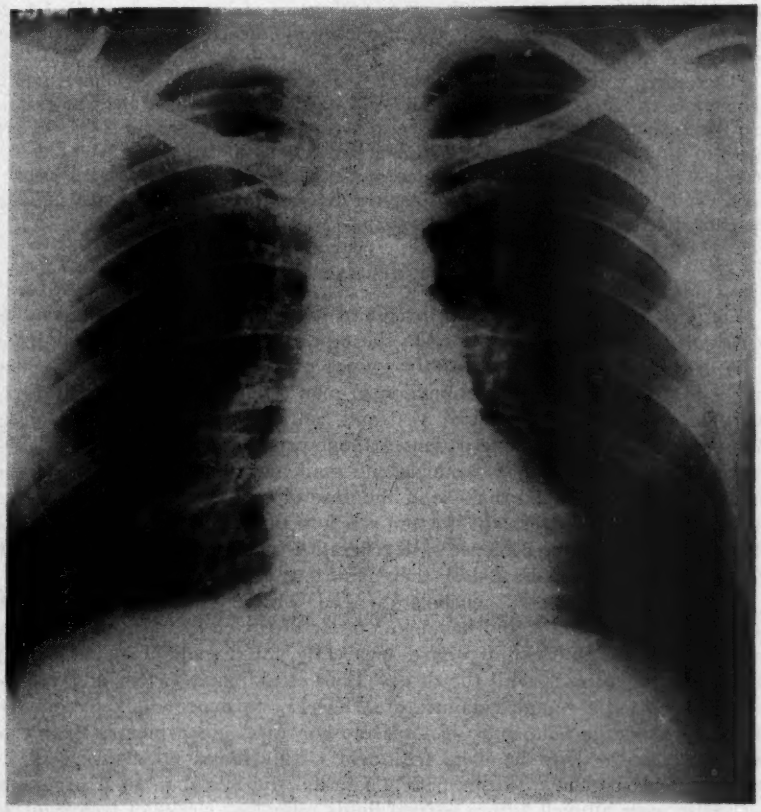

FIG. 2. X-ray of patient on February 10, 1956, after recovery. There is some residual fibrosis in the lungs, and the hilar lymph nodes are slightly enlarged.

manure. All of the mice were infected, and *H. capsulatum* was isolated from the mice.

The course in the hospital and the medication employed are shown graphically in chart 1. Penicillin, Achromycin and oxytetracycline were given before the possibility of psittacosis was eliminated. The patient was kept in an oxygen tent during the first six days of hospitalization. A second test with histoplasmin showed a more pronounced skin reaction than that obtained by his family physician in Florida,

suggesting that the allergic reaction in his lungs was becoming more intense. The anorexia continued and the dyspnea became more severe, even with maximal amounts of oxygen. At this point cortisone was administered to stop the allergic reaction in the lungs.

MRD-112 is fungicidal for *H. capsulatum* in the test tube, and there are several successful reports of its use in clinical cases in the literature.[6, 7] The MRD-112 was given in an effort to prevent the dissemination of the infection by cortisone. The dose was 300 mg. dissolved in 300 ml. of 5% dextrose in saline or 5% dextrose in distilled water. The drug was administered by a slow intravenous drip over a three- to five-hour period each day. Five milligrams of heparin were added to the intravenous fluid to prevent local thrombophlebitis. Penicillin and isoniazid were administered as prophylactic measures.

There was a dramatic reduction in the patient's dyspnea in 24 hours after the beginning of cortisone therapy. Within a few days he began to eat and was removed from the oxygen tent. He was discharged, asymptomatic, on August 28, 1955, after a gain of 12 pounds in weight. The indurated lesions in the lungs appeared to be somewhat smaller by x-ray at the time of discharge. A film made in Florida in February, 1956 (figure 2), showed complete disappearance of the original shadows. The patient returned to work and has remained well for the last 18 months.

Discussion

Large doses of cortisone have produced dissemination of experimental histoplasmosis in dogs [8] and mice.[9] On the other hand, there are several reports of no deleterious effects in mice [10] or guinea pigs.[11] Fox,[3] Shull [4] and Silverman et al.[5] have reported dissemination in man following the administration of cortisone. In contrast, Israel et al.[12] and Salvin and Furcolow [13] have each administered cortisone to one patient without producing a dissemination. The contradictory results in both animals and man may depend upon the state of immunity as well as upon the size of the dose of cortisone. Our patient probably had an effective degree of immunity before the cortisone was administered. This is suggested by the evidence of degeneration in the organisms seen in monocytes found in his sputum and by their failure to grow on suitable media.

Beta-di-ethyl-aminoethyl-fencholate (MRD-112) is fungicidal for *H. capsulatum* in the test tube, and has a low order of toxicity for several species of animals.[14] Ellis [6] and Sutliff [7] have apparently cured some acute disseminated cases of histoplasmosis with the drug. Polk et al.[15] and Lehan and his associates [16] reported a complete failure of MRD-112 to improve six patients with chronic progressive pulmonary histoplasmosis. More disturbing is their report of damage to the liver by drug treatment. Ellis found no evidence of liver damage in his patient. In our patient's serum the bilirubin, total protein and A-G ratio were all well within normal limits after two weeks of treatment with 300 mg. daily of MRD-112. In the cases reported by Polk et al. the damage to the liver may have been from the infection itself rather than from the MRD-112.

Michael and Vogel [17] used cortisone and MRD-112 in succession in a patient with acute pulmonary histoplasmosis. The patient had been diagnosed as sarcoidosis, and was treated with cortisone for 20 days before the correct diagnosis of histoplasmosis was established. The cortisone was discontinued and MRD-112 administered as soon as the fungus was isolated and identified. This patient recovered after a period of hospitalization of approximately three

months. There was an increase in the infection after cortisone was discontinued and before the MRD-112 was started.

Summary and Conclusions

Most patients with the epidemic type of pulmonary histoplasmosis recover without specific treatment. The mortality in over 400 cases collected by Lehan and Furcolow was only 1.2%. In the patient reported here, death was threatened by the almost complete consolidation of the lungs. Since the patient had a strongly positive skin test to histoplasmin, it was assumed that a considerable part of the pulmonary infiltration was the result of an allergic reaction to histoplasmin in the lungs. For this reason cortisone was administered to suppress the allergic reaction. Beta-di-ethyl-aminoethyl-fencholate (MRD-112) was administered in an effort to prevent the dissemination of the fungus which sometimes occurs following therapy with cortisone. The patient made a rapid recovery and has remained well for the last 18 months.

Acknowledgment

We wish to thank Dr. Nathaniel Thomson and Dr. Addison L. Messer, of St. Petersburg, Florida, for supplying us with the patient's history and record of treatment while in Florida.

Summario in Interlingua

In explorar un caverna, un masculo de racia blanc de 32 annos de etate esseva exponite a pulvere de stercore de vespertilion. Subsequentemente le fungo *Histoplasma capsulatum* esseva isolate ab le stercore. Symptomas pulmonar se manifestava tres septimanas post le exposition. Illos cresceva gradualmente in severitate, e illos non esseva afficite per therapia a antibioticos.

Le symptomas attingeva lor maximo de severitate a circa le tempore quando le test cutanee a histoplasmina deveniva positive. Le titro de anticorpore a fixation de complemento pro *H. capsulatum* in le sero esseva 1 : 128.

Ronchos pulmonar, dyspnea, e cyanose esseva sever e non alleviate marcatemente per le uso de un tenta a oxygeno.

Le autores se sentiva fortiate a considerar le morte como imminente ab obstruction mechanic in le alveolos in consequentia de un reaction allergic al productos del fungo. Illes se decideva a tractar le patiente con cortisona. Le droga fungicide beta-di-ethyl-aminoethyl-fencholato (MRD-112) esseva administrate pro prevenir le dissemination del fungo.

Le melioration esseva dramatic. Le cyanose e le dyspnea dispareva in 24 horas. Le patiente esseva removite ab le tenta a oxygeno in tres dies. Le pulmones se clarificava progressivemente e monstrava un normal aspecto roentgenographic in sex menses.

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ERRATA

In the February, 1958, issue of the ANNALS OF INTERNAL MEDICINE, on page 334, twelfth line down, the phrase, ". . . 33% lost 40 pounds or more," should be corrected to read, ". . . 31% lost 40 pounds or more."

On page 342, the first sentence of the second paragraph of the Summary, now reading: "Fifty-three per cent of those who began treatment lost over 20 pounds; 28% lost over 40 pounds," should be substituted by a sentence reading: "Fifty-nine per cent of those who began treatment lost over 20 pounds; 31% lost over 40 pounds."

EDITORIALS

THE ANNUAL SCIENTIFIC PROGRAM OF THE AMERICAN COLLEGE OF PHYSICIANS

The Committee on Program, with the approval of the Board of Regents, has decided to enlarge the scope of the scientific program of the American College of Physicians at the annual session in 1959. It is particularly eager to solicit and present material relating to:

1. Recently conducted clinical investigation
2. Original material in the basic medical sciences which relate to internal medicine
3. Original material in clinical internal medicine

The program of the College often has been characterized as appealing primarily to the internist in practice. Generally the program has not been thought of as one for the presentation of original contributions by investigators but perhaps more as a forum for "solicited" contributions only.

The Committee on Program hopes to alter these opinions and to enlarge the program by including in it at the annual session four sessions which will run simultaneously each afternoon and cover the following:

CLINICAL INVESTIGATION. So much outstanding work in this category is available each year that at present there is insufficient outlet for it in the programs of societies of clinical investigation and those of groups with special interests.

The Committee on Program proposes to initiate a session devoted to clinical investigation which each afternoon would give a program of ten-minute presentations of investigative work, probably by categories—cardiovascular, metabolic, pulmonary and renal, for example. Material to be presented by associates and young fellows of the College will be especially sought and that of guests will be welcome.

Such a program will also give many young associates, fellows and guests, as well as the whole College membership, opportunity to participate in and listen to an outstanding program in clinical investigation. Dr. J. D. Myers, professor of medicine at the University of Pittsburgh, will have charge of this activity for the Committee on Program.

BASIC MEDICAL SCIENCES WHICH RELATE TO INTERNAL MEDICINE. Basic medical sciences are the life blood of internal medicine, and an outstanding program concerning them will be presented during each of the afternoon and some of the morning sessions in the form of ten, fifteen or twenty-minute papers, symposia and review lectures of 45 minutes' duration. This is an excellent platform for the presentation of original contributions and we hope a program which will interest full-time men and young investigators as well as the many members of the College who attend the annual sessions. Dr. Robert H. Williams, professor of internal medicine, University of Washington, will be in charge of this activity for the Committee on Program.

ORIGINAL MATERIAL IN CLINICAL MEDICINE. Clinical studies including reports of original investigations will be presented in two separate sessions each afternoon in an attempt to cover widely the whole field of clinical internal medicine. These sessions, as in the past, will be of primary interest to clinicians and practicing physicians and the material will be presented in the form of symposia, individual or related papers of ten to fifteen minutes each and lectures. Development of this phase of the program will be under the able direction of Drs. J. M. Hayman, Jr., Thomas Findley, Carl V. Moore and E. Hugh Luckey.

The Committee on Program is soliciting titles and informative abstracts of approximately 250 words which should reach the College headquarters by August 31st.

As in the past, the morning program of the annual session will include (1) an outstanding TV session; (2) lectures; (3) hospital clinics in many of the important hospitals in Chicago; and (4) the ever popular panel discussions.

The annual meeting of the American College of Physicians should be the outstanding meeting in internal medicine in this country and the world. The program presented should cover the entire field of internal medicine. It should be a forum sought for by the full-time teacher and the young investigator as well as the internist in practice. Equally important, it should present much of interest to all of them. It is the hope of the Committee on Program that the development of a program in clinical investigation and the encouragement of original contributions in the basic medical sciences and clinical medicine will do just this. If it does, then the many young investigators and full-time teachers in internal medicine will develop or revive interest in the College, clinicians will be exposed to a broad program of education, and the American College of Physicians will strengthen teaching, research and practice in internal medicine and will itself be strengthened.

SPECIAL ANNOUNCEMENT

PAPERS FOR FORTIETH ANNUAL SESSION

April 20–24, 1959, Chicago

The Program Committee Desires Original Contributions Concerning:

1. **CLINICAL INVESTIGATION**

2. **BASIC MEDICAL SCIENCES as related to Internal Medicine**

3. **CLINICAL STUDIES AND OBSERVATIONS**

Please send titles, authors' names and informative abstracts of approximately 250 words for consideration by the Committee on Program

THE AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street, Philadelphia 4, Pennsylvania

By August 31, 1958

THE SYNDROME OF MINERALOCORTICOID EXCESS

THE effect of acute potassium deficiency on neuromuscular transmission and cardiac action is readily recognized and can be promptly repaired by administration of potassium salts. The consequences of long-standing potassium depletion, including both functional and anatomical changes in kidneys, heart and muscle are not so generally appreciated. Chronic depletion of potassium follows prolonged inability to ingest and absorb dietary potassium, or loss through persistent diarrhea or abuse of laxatives. Potassium may be lost in urine because of disease involving the renal tubules, or during dehydration, acidosis, or other disorders which impair normal renal conservation of potassium. Excessive "mineralocorticoid" action, due to increased secretion by the adrenal cortex or to exogenous corticosteroids, leads to potassium depletion with specific features which distinguish it from other forms of potassium loss.

When large doses of a typical mineralocorticoid, desoxycorticosterone, are given to patients without adrenals, sodium and water excretion are reduced, weight rises as extracellular fluid is accumulated; and if overdosage is continued, edema increases to anasarca, with signs resembling congestive cardiac failure.[1] In normal man, however, large doses of desoxycorticosterone are followed by only minor increases in body weight.[2] At first, sodium is retained, but after several days, normal sodium excretion is resumed despite continued administration of hormone. A normal secretion of the adrenal cortex is one requirement for the circulatory or renal readjustments which prevent undue accumulation of extracellular fluid. Although this homeostatic mechanism limits the increase in extracellular sodium, desoxycorticosterone induces continuous potassium loss in urine, and to a lesser extent in feces, so long as the diet contains ample sodium. Ammonium excretion in urine is increased without a fall in urine pH. If sodium intake is very low, these effects of mineralocorticoid excess on electrolyte balance are minimized or abolished.

These initial signs of mineralocorticoid excess are soon followed by further evidences of potassium depletion. There is increasing thirst, and large volumes of dilute urine appear.[3] Renal concentrating power is im-

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paired, though urine flow can still be reduced by water deprivation or injection of vasopressin. Lassitude, muscular weakness, paralysis, and disturbances of cardiac action may follow, especially if sodium chloride is added to the diet. Plasma sodium and bicarbonate are increased, while potassium and chloride concentrations are abnormally low. Tissue analyses of animals in this state show that cellular potassium has been substantially reduced and replaced by sodium.[4] The pathologic changes observed after mineralocorticoid excess closely resemble those found in experimental potassium deficiency.[5] Necrosis of myocardial fibers, as well as vacuolation and necrosis of renal epithelium, is present. Flattened cells, deposits of calcium about the renal epithelium and in casts, and dilated tubules are noted.

Arterial hypertension appears in some patients after administration of corticosteroids.[1] Other forms of potassium deficiency are generally associated with a fall in blood pressure, sometimes with vascular collapse.[6] Arterial pressure is more readily increased in animals with reduced functioning kidney substance. In these animals, the hypertensive effect of desoxycorticosterone is reduced by a diet low in sodium, is not corrected by added potassium, and is aggravated by added sodium chloride.[7] Nephrosclerosis commonly follows sustained hypertension of this type in animals.

An excess of cortisol (hydrocortisone) induces a variable group of symptoms and signs often designated "Cushing's syndrome." The appearance of hypertension, edema, polyuria, weakness, and hypokalemia with hypochloremic alkalosis demonstrates the mineralocorticoid effects of cortisol, which are usually accompanied by abnormal fat distribution, loss of muscle mass, weakness of connective tissue and blood vessels, altered organic metabolism, and other abnormalities. Most patients with adrenal cortical tumor show several signs of "Cushing's syndrome"; but in certain instances, the hypertensive, renal, and electrolyte abnormalities are so prominent, and

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the other signs so inapparent, that the diagnosis of nephritis may be considered.[8]

When aldosterone was discovered to be the most potent mineralocorticoid secreted by the adrenal cortex, the ouput of this new hormone was estimated in patients with hyperadrenocorticism due to tumor or hyperplasia. Some of these patients showed excess aldosterone excretion. Other patients, whose output of aldosterone was within normal limits, showed predominant evidences of mineralocorticoid effect, and, in rare instances, no recognized signs of "Cushing's syndrome" despite significantly increased excretion of 17-hydroxycorticoids. Evidently, mineralocorticoid actions are not dependent solely on aldosterone but may result from an excess of other adrenocortical hormones.

Adrenocortical carcinoma or bilateral hyperplasia commonly secretes an excess of several hormones, which may appear as 17-ketosteroids, 17-ketogenic steroids, 17-hydroxycorticoids, and aldosterone in urine, and may induce mixed biochemical and clinical patterns with elements of virilism, Cushing's syndrome, or mineralocorticoid excess. A clinical syndrome of uncomplicated mineralocorticoid excess was first recognized in a case of adrenocortical carcinoma.[9] No sign of Cushing's syndrome was evident, but all of the features of corticosteroid-induced potassium deficiency were present and were improved after potassium replacement. Urine contained twice normal amounts of 17-ketogenic steroids. When the primary tumor was removed, there was rapid improvement in all symptoms and signs, which unfortunately recurred with the development of metastases. This patient excreted a very large amount of aldosterone (200 μg. per day), as well as increased quantities of other corticosteroid metabolites.

Conn's comprehensive descriptions[10] of a case of isolated mineralocorticoid excess, due to adrenocortical adenoma, brought this syndrome into the full light of public interest. He correctly ascribed this advanced stage of potassium depletion to hyperadrenocorticism. The muscular weakness, paralysis, and tetany were related to hypokalemic alkalosis. Arterial pressure was usually increased, though some measurements were within the normal range. The urinary abnormalities were attributed to "kaliopenic nephropathy," with polyuria, isosthenuria resistant to pitressin, pH near 7.0, intermittent proteinuria, minimal abnormalities of urine sediment, and good

[8a] Plotz, C. M., Knowlton, A. I., and Ragan, C.: The natural history of Cushing's syndrome, Am. J. Med. **13**: 597, 1952.

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[10b] Conn, J. W., and Louis, L. H.: Primary aldosteronism, a new clinical entity, Ann. Int. Med. **44**: 1, 1956.

excretory function. Reduced concentrations of sodium in sweat and saliva were noted as evidence of extra-renal effects of circulating mineralocorticoid. The high renal clearance of potassium was found to reduce the effectiveness of potassium replacement, but not to abolish its beneficial effects. Surgical removal of a small adrenal cortical adenoma was followed by prompt, marked potassium retention and sodium elimination. Nephrosclerosis and tubular degeneration were found on renal biopsy. The blood pressure fell gradually to normal, while repair of renal concentrating power was slow and incomplete.

At least twenty additional cases of adenoma of the adrenal with predominant mineralocorticoid effects have been described since 1955.[11] * Some variations from the early descriptions have been noted. Early, heavy edema has been reported in a few cases without evident cause. Arterial pressure has varied from upper limits of normal to impressive increases with findings suggestive of a "malignant" or accelerated form. Heart failure and cerebrovascular accidents have occurred. Polydipsia and polyuria do not appear in every case, and some patients are able to concentrate urine to 1.020 or above.

Hyperplasia of the adrenal cortex was found in four patients,[12] aged 10 to 17. History of hyperpyrexia, convulsion, or other evidence of disorder of the nervous system suggested a possible disturbance of central regulation of aldosterone secretion. The signs of mineralocorticoid excess diminished after surgical removal of one or both adrenal glands.

Since excretion of 17-ketosteroids and 17-hydroxycorticoids was normal, while aldosterone output was greatly elevated, it was appropriate to apply

* Because of space limitations, only a few references are included here.

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[12a] van Buchem, F. S. P., Doorenbos, H., and Elings, H. S.: Primary aldosteronism due to adrenocortical hyperplasia, Lancet **2**: 335 and 574, 1956.

[12b] Holten, C., and Petersen, V. P.: Malignant hypertension with increased secretion of aldosterone and depletion of potassium, Lancet **2**: 918, 1956.

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the term, "primary aldosteronism," to Conn's case. This name is not applicable to other cases of identical character, whose urine contains quantities of aldosterone within or just at the upper limits of normal. Even in those cases with increased aldosterone secretion, the role of corticosterone and cortisol in pathogenesis of potassium loss may have been underestimated. Considerable amounts of corticosterone were found in those cases in which the adenoma was analyzed.[11] The adenomas from three typical cases of mineralocorticoid excess, incubated immediately after surgical excision, have produced much larger quantities of corticosterone and cortisol than of aldosterone.[11] It may be recalled that desoxycorticosterone causes largely extracellular sodium retention in patients without adrenals, while the presence of functioning adrenals protects to some extent against edema but favors potassium loss. Observations on adrenalectomized rats also suggest that a mixture of aldosterone with corticosterone or cortisol causes more potassium loss and less sodium retention than aldosterone given alone. Similar data are found in the "paradoxical" effect of cortisol and corticotrophin on sodium excretion in mineralocorticoid excess.

Secretion by a tumor of a mixture of hormones favoring potassium excretion rather than sodium retention could account for the hitherto unexplained difference between this potassium-losing syndrome, and the accumulation of edema which occurs in various diseases of heart, kidneys, or liver with a comparably increased output of aldosterone. Other explanations might involve a greater tendency of the latter group to retain water and sodium through local capillary imbalance, to collect this extracellular fluid in a relatively unavailable site, to fail to manifest the normal homeostatic responses to expansion of extracellular fluid, and to fail to eliminate the retained water and sodium because of impaired glomerular filtration and other factors favoring antidiuresis. Patients with idiopathic edema, which has no known cause except a persistently high aldosterone output, do not show any definite evidence of potassium deficiency. Edema might be thought to protect to some extent against replacement of intracellular potassium; but that such protection is incomplete is shown by the combined presence of edema and potassium depletion in a few cases of adrenal tumor.[11]

Differential diagnosis of mineralocorticoid excess from other forms of hyperadrenocorticism may be difficult because various mixtures of hormones produce mixed syndromes which defy simple classification. Here, we must be concerned not only with the clinical and laboratory findings and with the patterns of hormone secretion but also with the histopathology, which can be determined with certainty only by surgical exploration. There is also a curious mineralocorticoid-like syndrome associated with certain forms of carcinoma not arising in adrenal or pituitary glands.[13]

Forms of potassium deficiency not due to renal loss are readily dis-

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tinguished by the history of other causes and by the low concentration and output of potassium in urine. Other causes of urine potassium loss, including excessive cellular catabolism, diabetes mellitus, acidosis and dehydration, should become apparent during the general examination and ordinary study of blood and urine. Renal tubular acidosis should be ruled out by the distinctive hyperchloremia, acidosis, hypophosphatemia and tendency for serum sodium and calcium levels to be reduced. Most of these cases show arterial hypotension, as opposed to the hypertension of mineralocorticoid excess. The atypical findings and good response to conservative potassium therapy should distinguish other cases of renal disease with impaired function and hypertension, who lose potassium readily when potassium intake is cut off or diarrhea occurs.[14] Except for these cases, the diagnosis of "potassium-losing nephritis" should be viewed with suspicion, since a number of these cases have been shown to be due to adrenocortical tumors. A few published cases still escape definite classification because of a lack of data which are currently considered to be essential.

Some brilliant recoveries have followed surgical removal of an adenoma secreting an excess of mineralocorticoids; but in other instances, the patient is not returned to a normal state. Blood pressure may remain elevated, and the patient may be left with severe and irreversible disease of kidneys, heart, or brain. It is important to establish the diagnosis as early as possible so as to avoid the irreversible changes which follow potassium depletion and hypertension of long standing. There is also the possibility that a carcinoma of the adrenal is responsible for the overproduction of mineralocorticoids.

Two observations which have directed our attention to this syndrome have been muscular weakness and hypertension. Muscular weakness is ordinarily a late development and cannot be used for early case detection. Hypertension is probably not an immediate consequence, but the earliest diagnosis thus far was based on virtually asymptomatic hypertension. It is possible that in the initial stage, only asymptomatic hypokalemia might be present, but this would not be detected by any reasonable case-finding method.

It is too early as yet to state what the ultimate minimum requirements for diagnosis will be. The minimum findings necessary for diagnosis in the past may be excessive when viewed in light of information available today. For the time being, the key finding will probably be arterial hypertension. This may be asymptomatic and may appear benign during the early stage. A typical case would be a relatively young woman without obesity or renal disease or other cause for her hypertension. The blood pressure has not diminished significantly on symptomatic and medical man-

[14a] Elkinton, J. R., Tarail, R., and Peters, J. P.: Transfers of potassium in renal insufficiency, J. Clin. Investigation **28**: 378, 1949.

[14b] Schoch, H. K.: Potassium deficiency in chronic renal disease, Arch. Int. Med. **88**: 20, 1951.

[14c] Schwartz, W. B.: Potassium and the kidney, New England J. Med. **253**: 601, 1955.

agement. Findings do not suggest pheochromocytoma, and a Regitine test is normal. The response to ganglionic blocking agents is unsatisfactory.

The serum potassium concentration in advanced cases may be very low, but in other instances, borderline values have been obtained, and it may be necessary to do several fasting serum potassium determinations to get some idea of the range of variation. Although spontaneous return of serum potassium to normal on bed rest has been described in a case associated with adrenocortical tumor, in most instances it is necessary to administer potassium salts, often in very large quantities, before the serum potassium is satisfactorily increased. Normal subjects excrete practically all potassium which is added to an ordinary diet, so that no more than 100 mEq. are retained in the body over a period of several days even on very large doses. However, patients with potassium depletion of any consequence will usually retain much larger quantities, from 200 mEq. to above 1000 mEq. total. If unusually large amounts of the administered potassium are lost in the urine while serum potassium remains low, this is suggestive but not pathognomonic of mineralocorticoid excess. In the mildest cases, it may also be of some interest to note whether potassium loss occurs on a moderately low intake of potassium (40 to 50 mEq., for example). This might be dangerous for patients with severe deficiencies, but in those cases with serum potassium near normal, it may be necessary to place the patient on a reduced intake of potassium in order to demonstrate that potassium conservation by the kidney is inadequate. Moderate loss of potassium in the stools may occur in patients with excessive mineralocorticoid, since these hormones work on the gastrointestinal tract as well as on the renal tubules.

If alkalosis and hypochloremia are present, without other cause such as repeated vomiting or extra-renal potassium loss, it suggests mineralocorticoid effect. But serum sodium, carbon dioxide, and chloride may be normal in some cases of adrenal tumor.

Study of renal function may provide helpful information.[11] Polyuria and polydipsia are important, when present, but ordinary volumes of modestly concentrated urine may be excreted. Some limitation of concentrating power may be present, and the normal action of pitressin in raising urine osmolarity may fail, even though there is some effect on urine flow. Neutral pH and low titratable acidity are regularly present, together with an unexpectedly high urine ammonia excretion in freshly voided urine. Bacteria growing in urine, or active pyelonephritis, could lead to an alkaline urine with high pH, low titratable acidity, and a high ammonia. Such a strongly alkaline urine would not be typical of mineralocorticoid excess, in which the urine is more likely to be neutral. Urine cultures may be necessary to rule out an active urinary tract infection. Pyelonephritis and nephrosclerosis are possible late complications of mineralocorticoid excess.

Other evidence of mineralocorticoid excess is usually found in the form of reduced sodium concentration and increased potassium to sodium ratio

in sweat, saliva, and stool. The collection of thermal sweat is easily accomplished in a plastic bag. Salivary sodium and potassium concentrations are less well defined. There is considerable variation in normal individuals.[15]

Certain synthetic steroids appear to act as antagonists to aldosterone.[16] Preliminary observations suggest that these compounds may be helpful in assessing the role of aldosterone in various states. In one case with an adrenal adenoma, secreting aldosterone, corticosterone, and cortisol, and presenting the syndrome of mineralocorticoid excess, the administration of an aldosterone antagonist was followed by a sharp rise in sodium excretion and subsequent decrease in renal clearance of potassium.[17] It remains to be shown that similar changes occur consistently in other cases of mineralocorticoid excess, and not in other forms of potassium deficiency, before the diagnostic value of these new compounds can be assessed.

If an adrenal tumor is visible in roentgenograms, including tomograms, pyelograms, or films taken after insufflation of oxygen in the presacral area, this information will facilitate surgery. The decision to operate should not rest on the roentgenologist, since the tumor may be too small to demonstrate with any certainty. Any patient who shows the definitive pattern of mineralocorticoid excess should be explored. An adenoma may be very small and elusive even when the adrenals are exposed. Removal of a tumor responsible for excessive secretion will result in cure, provided that secondary structural changes have not taken place. Early case finding and differential diagnosis are essential for the best result.

JOHN A. LUETSCHER, JR., M.D.

[15a] Conn, J. W.: Electrolyte composition of sweat, Arch. Int. Med. **83**: 416, 1949.

[15b] Locke, W., Talbot, N. B., Jones, H. S., and Worcester, J.: Studies on the combined use of measurements of sweat electrolyte composition and rate of sweating as an index of adrenal cortical activity, J. Clin. Investigation **30**: 325, 1951.

[15c] Prader, A., Gautier, E., Gautier, R., Näf, D., Semer, J. M., and Rothschild, E. J.: The sodium and potassium concentration in mixed saliva: influence of secretion rate, stimulation, method of collection, age, sex, time of day, and adrenocortical activity, in The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology **8**: 382, 1955.

[15d] Berger, E. Y., Quinn, G. P., and Homer, M. A.: Effect of desoxycorticosterone on the colon: its relation to the action of cation exchange resins in man, Proc. Soc. Exper. Biol. and Med. **76**: 601, 1951.

[16a] Kagawa, C. M., Cella, J. A., and Van Arman, C. G.: Action of new steroids in blocking effects of aldosterone and desoxycorticosterone on salt, Science **126**: 1015, 1957.

[16b] Liddle, G. W.: Sodium diuresis induced by steroidal antagonists of aldosterone, Science **126**: 1016, 1957.

[17] The synthetic steroid, 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl) propionic acid γ-lactone, code number SC-5233, was furnished by the Division of Clinical Research, G. D. Searle and Company, through the kindness of Dr. I. C. Winter and Dr. C. L. Gantt.

REVIEWS

Cardiovascular Innervation. By G. A. G. MITCHELL, O.B.E., T.D., M.B., Ch.M., D.Sc., Professor of Anatomy and Director of the Anatomical Laboratories in the University of Manchester. 356 pages; 18 × 25.5 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, $11.00.

As stated in the foreword, "works on the anatomy of the nerve supplies of the cardiovascular system are few indeed and correct accounts rarer still. Yet the subject is of great importance to medicine and one of immense fascination to the clinician." This monograph is the product of an anatomist who has carried out extensive investigation in this field. While primarily anatomically oriented, the author has not tried to divorce structure from function. The result is a happy blending of much of our present-day knowledge of the neurovascular complex. There are chapters on the autonomic representation in various parts of the nervous system, both central and peripheral, on autonomic endings and pathways, both afferent and efferent, and on innervation of vessels and vascular structures in various parts of the body. The text is well organized, complete, and carefully written. The illustrations are excellently reproduced and clearly labeled. The selected bibliography is up to date and complete.

In a text such as this, one may select many statements for comment. In describing arterial post-ganglionic fibers, the author points out that local fluctuations in arterial blood flow are not produced solely by variations in the tonicity of the media as a result of vasomotor impulses, with consequent modifications in the lumina of the vessels, but that there are sphincter mechanisms in the arterial tree which all play a part in regulating the blood flow to any particular area or organ. He points out areas of controversy, such as the lack of agreement about the source of the presumed nerve fibers around capillaries. Citing the fact that comparatively recent investigations have shown that some intracranial vessels receive parasympathetic vasodilator fibers whereas formerly they were thought to possess only a sympathetic supply (dilatation of these vessels was being regarded as a sequel of diminished sympathetic activity), he asks whether similar views about the unisystemic innervation of other visceral structures may also be erroneous: "is our conception too limited, especially in regard to the distribution of parasympathetic nerves?" He describes findings which cast doubt on the common view that the nerve supply of the ventricles of the heart is entirely or predominantly sympathetic in nature.

This book is a valuable contribution. It should prove to be fascinating and useful reading for the cardiologist, neurologist, physiologist, and anatomist. It is highly recommended.

SIDNEY SCHERLIS, M.D.

EKG-Fibel. By Dr. Med. ROLF HEINECKER. 203 pages; 15.5 × 23 cm. (paperbound). Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, kartoniert DM 19.80.

In his primer on electrocardiography, Dr. R. Heinecker has been able to compress a large amount of most useful information into 200 pages. The presentation of the subject matter is very clear and informative. The presentation of basic physiology is very brief and schematic. There might be differences of opinion as to how much of a monograph should be apportioned to the discussion of basic electrophysiology. On the other hand, if the text is predominantly addressed to practicing physicians who need a general guide and instruction in the interpretation of clinically

encountered electrocardiograms, the basic electrophysiology might, with justification, be more neglected. The presentation of individual complexes and the discussion of their variation in the various electrocardiographic entities are superbly done, with brevity, but remarkable clarity. Sixty pages are assigned to a discussion of disturbances of impulse formation and arrhythmias. Here, too, the text is clear, brief and to the point. The very numerous illustrations are of excellent quality, particularly remarkable in that all of them were obtained with a multi-channel recorder, often with a simultaneously recorded phonocardiogram. The subject index is well organized and of unusual detail and usefulness.

The text can be highly recommended to the practicing physician with a good command of the German language.

A. G.

The Bacteriology of Tuberculosis. By EGONS DARZINS, M.D. 488 pages; 16 × 24 cm. University of Minnesota Press, Minneapolis. 1958. Price, $10.00.

The student of tuberculosis, the practitioner of medicine and the laboratorian concerned with the study of the tubercle bacillus will welcome the advent of Dr. Darzins' masterful summary of controversial and widely scattered facts about this disease. The author's stated objectives are a review of results already achieved in tuberculosis research and definition of many of the unsolved problems in this field. Both of these objectives have been accomplished with well organized and clearly stated data.

Dr. Darzins has divided this book into five sections each of which devotes an appropriate amount of time to the historical developments which have led to present day concepts. Morphology and cytology of the mycobacteria are discussed at length in part one, in which section, physical, biological and biochemical methods of studying the bacterial cell are described in detail. The second section deals with the metabolic activity of tubercle bacilli and summarizes numerous studies which have been concerned with the definition of growth requirements and the development of improved artificial media. Of greatest value to the clinician who must cope with the problem of human tuberculosis is the third section in which is presented an excellent account of methods employed in identifying tubercle bacilli as well as a critical analysis of the quantitative aspects of tuberculous infections. Methods of handling potentially infected material, the choice of decontaminants and use of various artificial media are discussed in great detail. Technical personnel concerned with the laboratory diagnosis of tuberculosis will find this section very enlightening. From a compilation of several thousands of tests performed in various laboratories, the author demonstrates the equality or, in some instances, the superiority of artificial media as compared with guinea pig inoculation.

Part four deals with the use of a variety of lower animals including the embryonated hen's egg in experimental tuberculosis. In this section the basic principles which apply to the evaluation of any new antituberculosis drug are outlined. The pathogenesis of tuberculosis in laboratory rodents and the application of these phenomena to drug tests and the study of human disease are discussed. Finally, this section describes the hazards of laboratory work with tubercle bacilli and the precautions to be taken.

The volume is well supplied with comprehensive tables of inestimable value as well as useful illustrations. Dr. Darzins is to be commended for drawing freely on other fields of microbiology for information he has considered essential. The task of compiling the large and yet selective bibliography has been an arduous one. Anyone who has an interest in the microbiological aspects of tuberculosis will find the reading of this book a profitable experience.

FRED R. MCCRUMB, JR., M.D.

Physical Methods in Physiology. By W. T. CATTON, M.Sc. 375 pages; 12.5 × 19.5 cm. Philosophical Library, N. Y. 1957. Price, $10.00.

In the preface, the author states: "This book is an attempt to present, in an abbreviated form, the wide variety of physical experimental techniques and theoretical treatments which have been applied to physiological investigations. Its terms of reference thus cover a part of the rather ill-defined field of biophysics. Such works on biophysics as are available relate generally to limited fields of specialized investigation, including the properties of protoplasm, the submicroscopical structure of cells and tissues, and osmotic and permeability phenomena in living systems. I have sought to cover a different and wider field, to include some mention of the main physical methods used in investigations in the major fields of physiology, and to deal also with physical treatment of physiological phenomena. Although the emphasis is on methods, an attempt has been made to include such fundamental physiology as will prevent the book becoming a mere catalogue of experimental techniques, and further to this end the chapters deal with recognized physiological 'systems.'"

The chapter headings show very well *how* this has been attempted. They are: Blood, The Circulation, Respiration, Muscle, Peripheral Nerve, The Physical Basis of Body Heat Exchanges, and Electronics in Physiology.

In the reviewer's opinion, the expressed attempt has been highly successful. This is a unique book—no other similar attempt is known. Considering that the author has pursued two major and difficult purposes—to present the physiologic principles of the system being measured as well as the principles of the methodology used, the effort is outstanding.

Particularly valuable is the selection of material. This is not a "cookbook," detailing many methods; rather, it is a compendium describing the principles of a relatively broad methodology that seem important to the author. Unfortunately, this approach has another side: It permits the author to leave gaps that some readers may wish had been filled. To name three of these: There is nothing about human energy metabolism, the physiology of respiratory exchange is incompletely covered and, finally, the principles of cardiac catheterization in animals and humans need describing by a person with Catton's grasp of fundamentals.

This is such a valuable book for persons making physical measurements of physiological systems, it is hoped that subsequent editions will be written and published soon, so that it is kept abreast of rapidly expanding knowledge.

B. W. A.

Fundamentals of Clinical Fluoroscopy and Essentials of Roentgen Interpretation. 2nd Ed. By CHARLES B. STORCH, M.D., Associate Attending Roentgenologist, Radiodiagnostic Department, Beth-El Hospital, Brooklyn, New York. 305 pages; 18 × 26 cm. Grune and Stratton, New York. 1957. Price, $8.75.

Fundamentals of Clinical Fluoroscopy and Essentials of Roentgen Interpretation has been revised and expanded in the second edition to include new methods and facts about subjects covered in the first edition, plus entirely new sections on congenital heart disease, the intestinal tract and the gall-bladder. This book is an excellent treatise from which a basic knowledge of clinical fluoroscopy may be obtained without the reader being lost in minutiae.

The author stresses the basic essentials of fluoroscopy in the normal and pathologic examination and has ably succeeded in presenting these essentials, including the limitations as well as the potentials of fluoroscopy. In each chapter, fundamentals of normal anatomy, contrast material, normal variants, positions, etc., are discussed prior to a discussion of various pathologic lesions. Differential diagnosis is stressed and fundamentals of roentgen interpretation often discussed.

The book is beautifully illustrated with both photographs and sketches, is easily read and is highly recommended to all students and physicians desiring to increase their knowledge of clinical fluoroscopy.

J. M. D.

Kohlenhydratstoffwechsel, Insulin und Diabetes. By PROF. DR. HANS STAUB. 48 pages; 15.5 × 23.5 cm. (paper-bound). Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, kartoniert, DM 9.60.

This little book is a valuable summary of the thinking of one of the great original investigators of diabetes and carbohydrate metabolism. Following a historical and clinical introduction of the endocrinology of diabetes, Dr. Staub discusses the controversial question of the "free diet" versus strict control and presents a fairly weak case for strict control. In a review of the history of the use of fructose in diabetes our attention is called to the fact that the first to report the difference in handling of the fructose and glucose was Minkowski. The conclusion of a learned review and analysis is that fructose is useless and contraindicated in the therapy of diabetes and of diabetic coma. The metabolism of ketone bodies is covered in a few pages and a short statement of the cause and treatment of diabetic coma follows. The author cites only three causes of coma—poor diet, inadequate insulin dosage, and infection, and does not go into them at all. He outlines therapy on the basis of estimating total glucose and giving one unit of insulin per gram. The use of the laboratory to follow therapy of coma is stressed. Glucagon is mentioned almost in passing and some attention is given the sulfanyl ureas as hypoglycemic agents. There is a review of the structure of insulin and the book closes with a consideration of the mechanism of insulin action. The author leans slightly toward the current permeability theory but calls attention to the binding of insulin to tissues as a factor of major importance.

It is unfortunate that this book is not available in English for it calls attention to some interesting old and new work by Europeans which has not received much notice in this country. It is a pleasure to read this masterful analysis of the problem.

SAMUEL P. BESSMAN, M.D.

The Doctor as a Witness. By JOHN EVARTS TRACY. 221 pages; 15 × 21 cm. W. B. Saunders Company, Philadelphia. 1957. Price, $4.25.

The author is Professor of Law, Emeritus, at the University of Michigan. His motive in writing the book is aptly expressed in these excerpts from the Preface—"This short volume was not written as a text for either medical school or law school use. It is purely informational, endeavoring to explain to the busy practitioner . . . the various kinds of legal proceedings in which he may be called to testify, how these proceedings are conducted and what is expected from a medical witness when he takes the stand."

It presents in twelve chapters of clearly written prose the need for expert witnesses, their preparation for testimony, the manner of testifying, many pitfalls which lead either to embarrassment of the witness or miscarriage of justice, the requisites of a good witness, the matter of compensation for time spent in studying and testimony concerning the case and a brief description of certain court sponsored experiments in the use of improvement of expert testimony by the "neutral" or court appointed witness.

This reviewer finds the book extremely readable, and full of helpful hints for conducting expert testimony as well as generally informative about court procedures. In these times, when the pace of medicolegal activities is so rapidly increasing and so many physicians are being called into court as witnesses in connection with

compensation or other insurance claims of their patients, or in their own defense in alleged malpractice, members of the profession will do well to learn more about being a witness. Tracy's book answers this need in an expert and at the same time inexpensive fashion.

R. S. F.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

African Conference on Bilharziasis, Brazzaville, French Equatorial Africa, 26 November-8 December 1956. World Health Organization Technical Report Series No. 139. 42 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Biographie und Klinik der Adipositas: Die Bedeutung von Gehirn und Psyche während Wachstum und Altern. By Doz. Dr. Günter Clauser. 166 pages; 24.5 × 16 cm. (paper-bound). 1958. Ferdinand Enke Verlag, Stuttgart. Price, Kartoniert DM 39.—.

A Contribution to the Study of Portal Hypertension. Jacksonian Prize Essay, Royal College of Surgeons 1956. By Alan Henderson Hunt, M.A., D.M., M.Ch., F.R.C.S., Surgeon St Bartholomew's Hospital and The Royal Marsden Hospital, etc. 230 pages; 25.5 × 18 cm. 1958. The Williams & Wilkins Co., Baltimore. Price, $8.50.

Consciousness and the Chemical Environment of the Brain: Report of the Twenty-fifth Ross Pediatric Research Conference. 109 pages; 23 × 15 cm. (paper-bound). 1958. Ross Laboratories, Columbus, Ohio. Available on request.

Endocrine Pathology of the Ovary. By John McLean Morris, M.D., Associate Professor of Gynecology, Yale University School of Medicine, New Haven, Connecticut; and Robert E. Scully, M.D., Clinical Associate in Pathology, Harvard Medical School, etc. 151 pages; 25.5 × 17.5 cm. 1958. The C. V. Mosby Company, St. Louis. Price, $8.50.

Enuresis: A Clinical and Genetic Study. (Acta Psychiatrica et Neurologica Scandinavica *Supplementum 114 Volumen 32.*) By Bertil Hallgren, M.D. 159 pages; 24.5 × 16.5 cm. (paper-bound). 1957. Ejnar Munksgaard, Copenhagen. Price, Da. Kr. 36.

Examen Pulmonaire de l'Asthmatique: Déductions Diagnostiques, Pronostiqués et Thérapeutiques. By Robert Tiffeneau. 245 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 2.300 fr.

Expert Committee on Addiction-Producing Drugs: Eighth Report. World Health Organization Technical Report Series No. 142. 12 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Group Processes: Transactions of the Third Conference, October 7, 8, 9, and 10, 1956, Princeton, N. J. Edited by Bertram Schaffner, M.D., University Seminar on

Communications, Columbia University, New York, N. Y. 328 pages; 24 × 16 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.00.

An International Nomenclature of Yaws Lesions. World Health Organization Monograph Series No. 36. By C. J. HACKETT, M.D., F.R.C.P., Medical Officer, Venereal Diseases and Treponematoses Section, World Health Organization; in cooperation with an International Group of Experts on Yaws and participants at the International Conference on Yaws Control, Enugu, Nigeria, 1955. 103 pages; 24.5 × 16 cm. (plastic-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $4.00.

Der Lungenboeck im Röntgenbild. By PROF. DR. KARL WURM, PROF. DR. H. REINDELL and PROF. DR. h. c. L. HEILMEYER. 220 pages; 27 × 18 cm. Georg Thieme Verlag, Stuttgart; available in U. S. A. and Canada from Intercontinental Medical Book Corporation, New York, N. Y. 1958. Price, Ganzleinen DM 78.—.

The Mammalian Cerebral Cortex. (Monographs of the Physiological Society, Number 5. Editors: H. BARCROFT, L. E. BAYLISS, A. L. HODGKIN.) By B. DELISLE BURNS, B.A. (Cantab.), M.R.C.S., L.R.C.P., Associate Professor of Physiology, McGill University, Montreal, Canada. 119 pages; 22 × 14 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $5.00.

The Medical World of the Eighteenth Century. By LESTER S. KING, M.D. 346 pages; 22 × 14.5 cm. 1958. The University of Chicago Press, Chicago. Price, $5.75.

Die Neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By PROF. DR. HERBERT REINDELL and DOZ. DR. HELMUTH KLEPZIG; mit einem Geleitwort von PROF. DR. DR. h. c. LUDWIG HEILMEYER. 192 pages; 24.5 × 17.5 cm. 1958. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York, N. Y. Price, Ganzleinen DM 29.50.

Polysaccharides in Biology: Transactions of the Second Conference, April 25, 26, and 27, 1956, Princeton, N. J. Edited by GEORG F. SPRINGER, M.D., William Pepper Laboratory of Clinical Medicine, Hospital and Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. 245 pages; 24 × 16 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $5.00.

La Roentgenthérapie des Affections Rhumatismales. By PIERRE PIZON. 275 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 2.800 fr.

Serological Reactions of Rheumatoid Arthritis: Summary of First Conference, January 23, 1957. 99 pages; 23 × 15 cm. (paper-bound). 1958. Issued by the Medical and Scientific Committee, Arthritis and Rheumatism Foundation, New York. Price, $1.00.

Textbook of Medical Treatment. 7th Ed. By Various Authors. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. Ed., F.R.C.P. Lond., Professor of Therapeutics and Clinical Medicine, University of Edinburgh, etc.; SIR STANLEY DAVIDSON, B.A. (Camb.), M.D., F.R.C.P. Ed., F.R.C.P. Lond., M.D. (Oslo), Physician, H. M. The Queen in Scotland, etc.; and S. ALSTEAD, M.D., F.R.C.P.

Ed., F.R.C.P. Lond., P.R.F.P.S., Regius Professor of Materia Medica and Therapeutics, Glasgow University. 924 pages; 24 × 17 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $11.00.

A Therapy for Anxiety Tension Reactions. By GERHARD B. HAUGEN, M.D., HENRY H. DIXON, M.D., and HERMAN A. DICKEL, M.D. 110 pages; 21.5 × 14.5 cm. 1958. The Macmillan Company, New York. Price, $3.50.

Use of Specifications for Pharmaceutical Preparations: Report of a Study Group. World Health Organization Technical Report Series No. 138. 29 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

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